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(54) Title: BENZAMIDES AND RELATED INHIBITORS OF FACTOR Xa

(57) Abstract: Novel benzamide compounds, their salts and compositions related thereto having activity against mammalian factor Xa are disclosed. The compounds are useful *in vitro* and *in vivo* for preventing or treating coagulation disorders.



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BENZAMIDES AND RELATED INHIBITORS OF FACTOR Xa

Cross Reference to Related Applications

This application claims benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/185,746 filed on February 29, 2000 and U.S. Provisional Application No. 60/154,332 filed on September 17, 1999 filed on September 17, 1999, each of which is herein incorporated in its entirety by reference.

Field of the Invention

This invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin). In another aspect, the present invention relates to novel monoamidino-containing compounds, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof which are useful as potent and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by coagulation disorders.

Background of the Invention

Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G., "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the

Blood Coagulation System", Blood Coag. Fibrinol. 5, 411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

5 A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active procoagulant thrombin. Unlike thrombin, which acts on a variety of protein substrates as well as at
10 a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* 15, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has been suggested that
15 compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see *e.g.*, WO 94/13693.

 Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent
20 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem., 263, 10162-10167 (1988). Another potent and highly
25 specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithodoros moubata*, as reported by Waxman, L., *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" *Science*, 248, 593-596 (1990).

 Factor Xa inhibitory compounds which are not large polypeptide-type
30 inhibitors have also been reported including: Tidwell, R.R. *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", *Thromb. Res.*, 19, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", *Biochemistry*, 25, 4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic Protease
35 Inhibitor (FUT-175) on the Coagulation System", *Haemostasis*, 15, 164-168 (1985);

Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", *Thromb. Res.*, 54, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", *Biochemistry*, 27, 2547-2557
5 (1988); Hauptmann, J. *et al.*, "*Comparison of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors*", *Thromb. Haemost.*, 63, 220-223 (1990); and the like.

Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino
10 substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)-NH₂ group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naphthyl group via a straight or branched chain alkylene, -C(=O) or -S(=O)₂ bridging
15 group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide
20 or carboxamide bridging group.

There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which
25 selectively inhibit factor Xa or its precursors. Compounds that have different combinations of bridging groups and functional groups than compounds previously discovered are needed, particularly compounds which selectively or preferentially bind to Factor Xa. Compounds with a higher degree of binding to Factor Xa than to thrombin are desired, especially those compounds having good bioavailability and/or
30 solubility.

Summary of the Invention

The present invention relates to novel compounds which inhibit factor Xa, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug
35 derivatives, and pharmaceutically acceptable compositions thereof which have

particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals characterized by undesired thrombosis or which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

In one embodiment, the present invention relates to a compound according to the formula:



wherein:

A is selected from:

(a) C_1 - C_6 -alkyl;

(b) C_3 - C_8 -cycloalkyl;

(c) $-N(R^1, R^2)$, $N(R^1, R^2)-C(=NR^3)-$, $N(R^1, R^2)-C(=NR^3)-N(R^4)-$, $R^1-C(=NR^3)-$, $R^1-C(=NR^3)-N(R^4)-$;

(d) phenyl, which is independently substituted with 0-2 R substituents;

(e) naphthyl, which is independently substituted with 0-2 R substituents;

and

a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are

selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substituents;

R is selected from:

- 5 H, halo, -CN, -CO₂R¹, -C(=O)-N(R¹, R²), -(CH₂)_m-CO₂R¹, -(CH₂)_m-C(=O)-N(R¹, R²), -NO₂, -SO₂N(R¹, R²), -SO₂R¹, -(CH₂)_mNR¹R², -(CH₂)_m-C(=NR³)-R¹, -(CH₂)_m-C(=NR³)-N(R¹, R²), -(CH₂)_m-N(R⁴)-C(=NR³)-N(R¹, R²), -(CH₂)_mNR¹- group appended to a 3 to 6 membered heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CF₃, -OR², and a 5-6
- 10 membered heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C₁-C₄-alkyl, -C₁₋₄alkyl-CN, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;
- 15

m is an integer of 0-2;

R¹, R², R³ and R⁴ are independently selected from the group consisting of:

- 20 H, -OR⁵, -N(-R⁵, -R⁶), -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂; or
- 25

- R¹ and R², or R² and R³ taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C₁-C₄-alkyl, -CN, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;
- 30

R⁵ and R⁶ are independently selected from the group consisting of:

H, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂; or

R⁵ and R⁶ taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -CN, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

Q is a member selected from the group consisting of:

a direct link, -CH₂-, -C(=O)-, -O-, -N(R⁷)-, -N(R⁷)CH₂-, -CH₂N(R⁷)-, -C(=NR⁷)-, -C(=O)-N(R⁷)-, -N(R⁷)-C(=O)-, -S-, -SO-, -SO₂-, -SO₂-N(R⁷)- and -N(R⁷)-SO₂-;

R⁷ is selected from:

H, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

D is a direct link or is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;
- (b) naphthyl, which is independently substituted with 0-2 R^{1a} substituents; and
- (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are

selected from N, O and S, and wherein the ring system may be substituted from 0-2 R^{1a} substituents;

R^{1a} is selected from:

- 5 halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, -(CH₂)_nNR^{2a}R^{3a}, -(CH₂)_nCO₂R^{2a}, -(CH₂)_nCONR^{2a}R^{3a}, -SO₂NR^{2a}R^{3a}, -SO₂R^{2a}, -CF₃, -OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be
- 10 independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂.

R^{2a} and R^{3a} are independently selected from the group consisting of:

- 15 H, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of
- 20 halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

n is an integer of 0-2;

E is a direct link or a member selected from the group consisting of:

- 25 -C₁₋₂-alkyl-, -O-, -S-, -SO-, -SO₂-, -C₀₋₁-alkyl-C(=O), -C₀₋₁-alkyl-C(=O)-N(-R⁸)-C₀₋₁-alkyl-, -C₀₋₁-alkyl-N(-R⁸)-C(=O)-C₀₋₁-alkyl-, -N(-R⁸)-C(=O)-N(-R⁸)- and -C₀₋₁-alkyl-N(-R⁸)-;

R⁸ is a member selected from the group consisting of:

- 30 H; -C₁₋₄-alkyl; -C₀₋₄-alkylaryl; -C₀₋₄-alkyl-heteroaryl; -C₁₋₄-alkyl-C(=O)-OH, -C₁₋₄-alkyl-C(=O)-O-C₁₋₄-alkyl, and -C₁₋₄-alkyl-C(=O)-N(-R^{2b}, -R^{3b});

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

- 35 H, -C₁₋₄-alkyl, -C₀₋₄-alkyl-aryl; -C₀₋₄-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered

heterocyclic ring containing 1-4 heteroatoms selected from N, O and S,
wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

- 5 Halo; -C₁₋₄-alkyl; -CN, -NO₂; -C(=O)-N(-R^{2c}, -R^{3c}); -C(=O)-OR^{2c};
 -(CH₂)_q-N(-R^{2c}, -R^{3c}); -SO₂-N(-R^{2c}, -R^{3c}); -SO₂R^{2c}; -CF₃ and -(CH₂)_q-OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:
H; -C₁₋₄-alkyl and -C₁₋₄-alkyl-aryl;

10

q is an integer of 0-2;

G is a member selected from the group consisting of:

- 15 (a) C₂-alkenyl or C₃₋₈-cycloalkenyl, wherein the alkenyl and cycloalkenyl
 attachment points are the alkenyl carbon atoms and wherein the -C₂-
 alkenyl or -C₃₋₈-cycloalkenyl are substituted with 0-4 R^{1d} groups;
- 20 (b) a phenylene group wherein the ring carbon atoms of the phenylene
 group are substituted with 0-4 R^{1d} groups;
- 25 (c) a 3-8 membered a saturated, partially unsaturated or aromatic
 monocyclic- heterocyclic ring system containing 1-4 heteroatoms
 selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic
 ring may be substituted with 0-4 R^{1d} groups; and,
- (d) an 8-10 membered fused heterocyclic bicyclic ring system, containing
 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of
 the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

- 30 H, halo; C₁₋₆-alkyl, carbocyclic aryl, -CN; -NO₂; -(CH₂)₀₋₆-NR^{2d}R^{3d};
 -SO₂NR^{2d}R^{3d}; -SO₂R^{2d}; -CF₃; -(CH₂)₀₋₆-OR^{2d}; -O-(CH₂)₁₋₆OR^{2d}; -O-(CH₂)₁₋₆-
 C(=O)-O-R^{2d};
 -O-(CH₂)₁₋₆-C(=O)-N(R^{2d}, R^{3d}); -N(R^{5a})-(CH₂)₁₋₆-OR^{2d};
 -N(R^{5a})-(CH₂)₁₋₆-N(R^{2d}, R^{3d}); -C(=O)-N(R^{2d}, R^{3d});
35 -N(R^{5a})-(CH₂)₁₋₆-C(=O)-N(R^{2d}, R^{3d}); -N(-(CH₂)₁₋₆-OR^{2d})₂; -N(R^{5a})-(CH₂)₁₋₆-OR^{2d};

$-N(R^{5a})-C(=O)-R^{2d}$; $-N(R^{5a})-SO_2-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-O-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-N(R^{2d}, R^{3d})$; $-(CH_2)_{0-6}-C(=NR^{2d})-N(R^{3d}, R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d}, R^{4d})$; a $-(CH_2)_{0-6}-N(R^{3d})C_{5-6}$ membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a $-(CH_2)_{0-5}-5-6$ membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{5a} , R^{2d} , R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C_{1-6} -alkyl and C_{1-6} -alkylaryl, -CN; -NO₂; carbocyclic aryl, -CN; -NO₂; or

R^{2d} and R^{3d} taken together with the N atoms they are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

J is a direct link or is a member selected from the group consisting of:

$-N(-R^9)-C(=O)-$; $-C(=O)-N(-R^9)-$; -O-; -S-; -SO-; -SO₂-; -CH₂-; -N(-R⁹)-; and $-N(-R^9)-SO_2-$;

R^9 is a member selected from the group consisting of:

H; $-C_{1-4}$ -alkyl; $-C_{0-4}$ -alkyl-carbocyclic aryl; $-(CH_2)_{0-4}-5-6$ membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S; $-(CH_2)_{1-6}-C(=O)-O-C_{1-4}$ -alkyl; and $-(CH_2)_{1-6}-C(=O)-N(R^{6a}, R^{6b})$;

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:

H and $-C_{1-6}$ -alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

- (b) naphthyl substituted with 0-3 R^{1e} groups and
- (c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and
- (d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

- Halo; CF₃; -C₁₋₄-alkyl; carbocyclic aryl; -C₀₋₂-alkyl-CN; -O-R^{2e}; -C₀₋₂-alkyl-C(=O)-O-R^{2e}; -C₀₋₂-alkyl-C(=O)-N(R^{2e}, R^{3e}); -C₀₋₂-alkyl-NO₂; -C₀₋₂-alkyl-N(R^{2e}, R^{3e}); -C₀₋₂-alkyl-SO₂-N(R^{2e}, R^{3e}); -C₀₋₂-alkyl-SO₂-R^{2e}; trihaloalkyl; -O-C₀₋₂-alkyl-O-R^{2e}; -C₀₋₂-alkyl-O-R^{2e}; -O-C₁₋₄-alkyl-C(=O)-N(R^{2e}, R^{3e}); -O-C₁₋₄-alkyl-C(=O)-O-R^{2e}; -C₀₋₂-alkyl-N(R^{2e})-C(=O)-R^{3e}; -C₀₋₂-alkyl-N(-R^{2e})-SO₂-R^{3e}; -CH₂-N(R^{2e})-C(=O)-R^{3e}; -CH₂-N(R^{2e})-SO₂-R^{3e}; -(CH₂)₀₋₆-NR^{2e}R^{3e}; -C(=O)-N(R^{2e}, R^{3e}); -N(-(CH₂)₁₋₆-OR^{2e})₂; -N(R¹⁰)-(CH₂)₁₋₆-OR^{2e}; -N(R¹⁰)-C(=O)-R^{2e}; -N(R¹⁰)-SO₂-R^{2e}; -C(=N(R¹⁰))-N(R^{2e}, R^{3e}); and a -(CH₂)₀₋₆-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R¹⁰, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

- H; -C₁₋₄-alkyl; -C₀₋₂-alkyl-O-R^{1g}; -C₀₋₂-alkyl-N(-R^{1g}, -R^{2g}); -C₁₋₄-alkyl-carbocyclic aryl; -C₁₋₄-alkyl-heterocyclic; and R¹⁰ and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are independently a member selected from the group of:

- H; halo; -C₁₋₄-alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -C(=O)-N(R^{3g})R^{4g}; -C(=O)-OR^{3g}; -NO₂; -(CH₂)_p-NR^{3g}R^{4g}; -SO₂NR^{3g}R^{4g}; -SO₂R^{3g}; -CF₃; and -(CH₂)_pOR^{3g};

p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

5 H; C₁₋₄-alkyl and -C₀₋₄-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

10 In certain aspects of this invention, compounds are provided which are useful as diagnostic reagents. In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the above
15 compounds and pharmaceutical compositions for preventing or treating disease states characterized by undesired thrombosis or disorders of the blood coagulation process in mammals, or for preventing coagulation in stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an
20 antithrombotic and/or a thrombolytic agent and/or an anticoagulant.

Detailed Description of the Invention

Definitions

25 In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkinyl" (or "alkynyl") refers to a straight or
30 branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified alkenyl and alkinyl each refer to radicals having from 2-12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain,
35 branched-chain and cyclic groups having the number of carbon atoms specified, or if

no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms.

5 As used herein, the terms "carbocyclic ring structure " and " C₃₋₁₆ carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of: a stable
10 monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic and ring structures in which both of the rings are non-aromatic; and a
15 stable tricyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic
20 ring structure may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), 2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or
25 tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents
30 indicated for that structure if such substitution(s) would result in a stable compound.

 The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy,
35 halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl,

carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, naphthyl, biphenyl, phenanthrenyl and naphthacenyl.

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The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydril, trityl, and the like, all of which may be optionally substituted.

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As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is intended to mean a substituted or unsubstituted member selected from the group consisting of stable monocyclic ring having from 5-7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen

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atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more than 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

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Examples of monocyclic and bicyclic heterocyclic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocyclic ring structures.

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As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

The term "methylene" refers to $-CH_2-$.

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary,

secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

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"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention that are often shown by *in vitro* assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

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In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

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Preferred Embodiments

In a preferred embodiment the present invention provides a compound according to the formula:



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wherein:

A is selected from:

- (a) C₁-C₆-alkyl;
- (b) C₃-C₈-cycloalkyl;
- (c) -N(R¹,R²), N(R¹,R²)-C(=NR³)-, N(R¹,R²)-C(=NR³)-N(R⁴)-, R¹-C(=NR³)-, R¹-C(=NR³)-N(R⁴)-;
- (d) phenyl, which is independently substituted with 0-2 R substituents;
- (e) naphthyl, which is independently substituted with 0-2 R substituents;
- (f) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substituents;

R is selected from:

- H, halo, -CN, -CO₂R¹, -C(=O)-N(R¹, R²), -(CH₂)_m-CO₂R¹, -(CH₂)_m-C(=O)-N(R¹, R²), -NO₂, -SO₂N(R¹, R²), -SO₂R¹, -(CH₂)_mNR¹R², -(CH₂)_m-C(=NR³)-R¹, -(CH₂)_m-C(=NR³)-N(R¹,R²), -(CH₂)_m-N(R⁴)-C(=NR³)-N(R¹,R²), -(CH₂)_mNR¹-C₃₋₆heterocyclics, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CF₃, -OR², and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C₁-C₄-alkyl, CN-C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

m is an integer of 0-2;

R¹, R², R³ and R⁴ are independently selected from the group consisting of:

- H, -OR⁵, -N(-R⁵, -R⁶), -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from

1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂; or

5

R¹ and R², or R² and R³ taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C₁-C₄-alkyl, -CN -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

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15 R⁵ and R⁶ are independently selected from the group consisting of:

H, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂; or

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R⁵ and R⁶ taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C₁-C₄-alkyl, -CN -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

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Q is a member selected from the group consisting of:

a direct link, -CH₂-, -C(=O)-, -O-, -N(R⁷)-, -N(R⁷)CH₂-, -CH₂N(R⁷)-, -C(=NR⁷)-, -C(=O)-N(R⁷)-, -N(R⁷)-C(=O)-, -S-, -SO-, -SO₂-, -SO₂-N(R⁷)- and -N(R⁷)-SO₂-;

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R⁷ is selected from:

- H, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

D is a direct link or is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;
- (b) naphthyl, which is independently substituted with 0-2 R^{1a} substituents; and
- (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted from 0-2 R^{1a} substituents;

R^{1a} is selected from:

- halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, -(CH₂)_nNR^{2a}R^{3a}, -(CH₂)_nCO₂R^{2a}, -(CH₂)_nCONR^{2a}R^{3a}, -SO₂NR^{2a}R^{3a}, -SO₂R^{2a}, -CF₃, -OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

R^{2a} and R^{3a} are independently selected from the group consisting of:

- H, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of

halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

n is an integer of 0-2;

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E is a direct link or a member selected from the group consisting of:

-C₁₋₂-alkyl-, -O-, -S-, -SO-, -SO₂-, -C₀₋₁-alkyl-C(=O), -C₀₋₁-alkyl-C(=O)-N(-R⁸)-C₀₋₁-alkyl-, -C₀₋₁-alkyl-N(-R⁸)-C(=O)-C₀₋₁-alkyl-, -N(-R⁸)-C(=O)-N(-R⁸)- and -C₀₋₁-alkyl-N(-R⁸)-;

10

R⁸ is a member selected from the group consisting of:

H; -C₁₋₄-alkyl; -C₀₋₄-alkylaryl; -C₀₋₄-alkyl-heteroaryl; -C₁₋₄-alkyl-C(=O)-OH, -C₁₋₄-alkyl-C(=O)-O-C₁₋₄-alkyl, and -C₁₋₄-alkyl-C(=O)-N(-R^{2b}, -R^{3b});

- 15 R^{2b} and R^{3b} are each a member independently selected from the group consisting of: H, -C₁₋₄-alkyl, -C₀₋₄-alkyl-aryl; -C₀₋₄-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

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R^{1c} is a member selected from the group consisting of:

Halo; -C₁₋₄-alkyl; -CN, -NO₂; -C(=O)-N(-R^{2c}, -R^{3c}); -C(=O)-OR^{2c}; -(CH₂)_q-N(-R^{2c}, -R^{3c}); -SO₂-N(-R^{2c}, -R^{3c}); -SO₂R^{2c}; -CF₃ and -(CH₂)_q-OR^{2c};

- 25 R^{2c} and R^{3c} are each independently a member selected from the group consisting of: H; -C₁₋₄-alkyl and -C₁₋₄-alkyl-aryl;

q is an integer of 0-2;

- 30 G is a member selected from the group consisting of:

(a) C₂-alkenyl or C₃₋₈-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein C₂-alkenyl or C₃₋₈-cycloalkenyl are substituted with 0-4 R^{1d} groups;

- (b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;
- (c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,
- (d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

- H, halo; C_{1-6} -alkyl, carbocyclic aryl, -CN; -NO₂; -(CH₂)₀₋₆-NR^{2d}R^{3d};
 -SO₂NR^{2d}R^{3d}; -SO₂R^{2d}; -CF₃; -(CH₂)₀₋₆-OR^{2d}; -O-(CH₂)₁₋₆OR^{2d}; -O-(CH₂)₁₋₆-C(=O)-O-R^{2d};
 -O-(CH₂)₁₋₆-C(=O)-N(R^{2d},R^{3d}); -N(R^{5a})-(CH₂)₁₋₆-OR^{2d};
 -N(R^{5a})-(CH₂)₁₋₆-N(R^{2d},R^{3d}); -C(=O)-N(R^{2d},R^{3d});
 -N(R^{5a})-(CH₂)₁₋₆-C(=O)-N(R^{2d},R^{3d}); -N(-(CH₂)₁₋₆-OR^{2d})₂; -N(R^{5a})-(CH₂)₁₋₆-OR^{2d};
 -N(R^{5a})-C(=O)-R^{2d}; -N(R^{5a})-SO₂-R^{2d}; -(CH₂)₀₋₆-C(=O)-O-R^{2d}; -(CH₂)₀₋₆-C(=O)-N(R^{2d},R^{3d}); -(CH₂)₀₋₆-C(=NR^{2d})-N(R^{3d},R^{4d});
 -(CH₂)₀₋₆-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d}); and -(CH₂)₀₋₆-N(-R^{3d})- group attached directly by its nitrogen atom to a carbon atom of a 5 to 6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a -(CH₂)₀₋₆- group attached to a 5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{5a} , R^{2d} , R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

- H, C_{1-6} -alkyl and C_{1-6} -alkylaryl, -CN; -NO₂; carbocyclic aryl, -CN; -NO₂; or

R^{2d} and R^{3d} taken together with the N atoms ther are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

- 5 J is a direct link or is a member selected from the group consisting of:
 $-N(-R^9)-C(=O)-$; $-C(=O)-N(-R^9)-$; $-O-$; $-S-$; $-SO-$; $-SO_2-$; $-CH_2-$; $-N(-R^9)-$; and
 $-N(-R^9)-SO_2-$;

R^9 is a member selected from the group consisting of:

- 10 H; $-C_{1-4}$ -alkyl; $-C_{0-4}$ -alkyl-carbocyclic aryl; $-(CH_2)_{0-4}$ -5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S; $-(CH_2)_{1-6}-C(=O)-O-C_{1-4}$ -alkyl; and $-(CH_2)_1$ -
 $_6-C(=O)-N(R^{6a}, R^{6b})$;

- 15 R^{6a} and R^{6b} are each a member independently selected from the group consisting of:
H and $-C_{1-6}$ -alkyl;

X is a member selected from the group consisting of:

- (a) phenyl substituted with 0-3 R^{1e} groups;
20 (b) naphthyl substituted with 0-3 R^{1e} groups and
(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and
25 (d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

- 30 R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3 ; $-C_{1-4}$ -alkyl; carbocyclic aryl; $-C_{0-2}$ -alkyl-CN; $-O-R^{2e}$;
 $-C_{0-2}$ -alkyl- $C(=O)-O-R^{2e}$; $-C_{0-2}$ -alkyl- $C(=O)-N(R^{2e}, R^{3e})$; $-C_{0-2}$ -alkyl- NO_2 ;
 $-C_{0-2}$ -alkyl- $N(R^{2e}, R^{3e})$; $-C_{0-2}$ -alkyl- $SO_2-N(R^{2e}, R^{3e})$; $-C_{0-2}$ -alkyl- SO_2-R^{2e} ;
35 trihaloalkyl; $-O-C_{0-2}$ -alkyl- $O-R^{2e}$; $-C_{0-2}$ -alkyl- $O-R^{2e}$; $-O-C_{1-4}$ -alkyl-

$C(=O)-N(R^{2e}, R^{3e})$; $-O-C_{1-4}-alkyl-C(=O)-O-R^{2e}$; $-C_{0-2}-alkyl-N(R^{2e})-C(=O)-R^{3e}$;
 $-C_{0-2}-alkyl-N(-R^{2e})-SO_2-R^{3e}$; $-CH_2-N(R^{2e})-C(=O)-R^{3e}$; $-CH_2-N(R^{2e})-SO_2-R^{3e}$;
 $-(CH_2)_{0-6}-NR^{2e}R^{3e}$; $-C(=O)-N(R^{2e}, R^{3e})$; $-N(-(CH_2)_{1-6}-OR^{2e})_2$; $-N(R^{10})-(CH_2)_{1-6}-OR^{2e}$;
 $-N(R^{10})-C(=O)-R^{2e}$; $-N(R^{10})-SO_2-R^{2e}$; $-C(=N(R^{10}))-N(R^{2e}, R^{3e})$; and a
 5 $-(CH_2)_{0-6}$ -5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10} , R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

10 H; $-C_{1-4}-alkyl$; $-C_{0-2}-alkyl-O-R^{1g}$; $-C_{0-2}-alkyl-N(-R^{1g}, -R^{2g})$; $-C_{1-4}-alkyl-carbocyclic aryl$; $-C_{1-4}-alkyl-heterocyclic$; and R^{10} and R^{2e} , or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

15 R^{1g} and R^{2g} are independently a member selected from the group of:

H; halo; $-C_{1-4}-alkyl$, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; $-CN$; $-C(=O)-N(R^{3g})R^{4g}$; $-C(=O)-OR^{3g}$; $-NO_2$;
 $-(CH_2)_p-NR^{3g}R^{4g}$; $-SO_2NR^{3g}R^{4g}$; $-SO_2R^{3g}$; $-CF_3$; and $-(CH_2)_pOR^{3g}$;

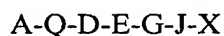
20 p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

25 H; $C_{1-4}-alkyl$ and $-C_{0-4}-alkyl-carbocyclic aryl$;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

30 In a further preferred embodiment the present invention provides a compound according to the formula:



wherein:

A is selected from:

(a) $C_1-C_6-alkyl$;
 35

- (b) C₃-C₈-cycloalkyl;
- (c) -N(R¹,R²), N(R¹,R²)-C(=NR³)-, N(R¹,R²)-C(=NR³)-N(R⁴)-, R¹-C(=NR³)-, R¹-C(=NR³)-N(R⁴)-;
- (d) phenyl, which is independently substituted with 0-2 R substituents;
- (e) naphthyl, which is independently substituted with 0-2 R substituents;
- and
- (f) monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substituents;

R is selected from:

H, halo, -CN, -CO₂R¹, -C(=O)-N(R¹, R²), -(CH₂)_m-CO₂R¹, -(CH₂)_m-C(=O)-N(R¹, R²), -NO₂, -SO₂N(R¹, R²), -SO₂R¹, -(CH₂)_mNR¹R², -(CH₂)_m-C(=NR³)-R¹, -(CH₂)_m-C(=NR³)-N(R¹,R²), -(CH₂)_m-N(R⁴)-C(=NR³)-N(R¹,R²), -(CH₂)_mNR¹- group attached to a 3-6 membered heterocyclic ring having from 1 to 3 heteroatoms selected from the group consisting of N, O and S, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CF₃, -OR², and a 5-6 membered heterocyclic aromatic or partially saturated system, including imidazoline, containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -methyl, -C₂-C₄-alkyl, -CN, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

m is an integer of 0-2;

R¹, R², R³ and R⁴ are independently selected from the group consisting of:

H, -OR⁵, -N(-R⁵, -R⁶), -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties

may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂; or

- 5 R¹ and R², or R² and R³ taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a
- 10 member selected from the group consisting of halo, C₁-C₄-alkyl, -CN -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

R⁵ and R⁶ are independently selected from the group consisting of:

- 15 H, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of
- 20 halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂; or

- R⁵ and R⁶ taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from
- 25 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C₁-C₄-alkyl, -CN -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

- 30 Q is a member selected from the group consisting of:
a direct link, -CH₂-, -C(=O)-, -O-, -NH-, -NMe-, -NHCH₂-, -NMeCH₂-, -CH₂NH-, -C(=NH)-, -C(=O)-NH-, -NH-C(=O)-, -CH₂NMe-, -C(=NMe)-;

D is a direct link or is a member selected from the group consisting of:

- 35 (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substituents; and

5 a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted from 0-2 R^{1a} substituents;

R^{1a} is selected from:

10 halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, -(CH₂)_nNR^{2a}R^{3a}, -(CH₂)_nCO₂R^{2a}, -(CH₂)_nCONR^{2a}R^{3a}, -SO₂NR^{2a}R^{3a}, -SO₂R^{2a}, -CF₃, -OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein
15 from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

R^{2a} and R^{3a} are independently selected from the group consisting of:

20 H, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of
25 halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

n is an integer of 0-2;

E is a member selected from the group consisting of:

30 a direct link, -O-, -NH-, -CH₂NH-, -NHCH₂-, -NMe-, -NH-C(=O)-NH-, -C(=O)-NH-, -NH-C(=O)-;

G is a member selected from the group consisting of:

35 (a) a C₂-alkenyl group or a C₃₋₈-cycloalkenyl group, wherein the alkenyl group and cycloalkenyl group attachment points are the alkenyl carbon

atoms and wherein the C₂-alkenyl group or C₃₋₈-cycloalkenyl group is substituted with 0-4 R^{1d} groups;

- (b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;
- (c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,
- (d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

- H, halo; C₁₋₆-alkyl, carbocyclic aryl, -CN; -NO₂; -(CH₂)₀₋₆-NR^{2d}R^{3d}, -SO₂NR^{2d}R^{3d}, -SO₂R^{2d}, -CF₃; -(CH₂)₀₋₆-OR^{2d}; -O-(CH₂)₁₋₆OR^{2d}; -O-(CH₂)₁₋₆-C(=O)-O-R^{2d};
- O-(CH₂)₁₋₆-C(=O)-N(R^{2d},R^{3d}); -N(R^{5a})-(CH₂)₁₋₆-OR^{2d};
- N(R^{5a})-(CH₂)₁₋₆-N(R^{2d},R^{3d}); -C(=O)-N(R^{2d},R^{3d});
- N(R^{5a})-(CH₂)₁₋₆-C(=O)-N(R^{2d},R^{3d}); -N(-(CH₂)₁₋₆-OR^{2d})₂; -N(R^{5a})-(CH₂)₁₋₆-OR^{2d};
- N(R^{5a})-C(=O)-R^{2d}; -N(R^{5a})-SO₂-R^{2d}; -(CH₂)₀₋₆-C(=O)-O-R^{2d}; -(CH₂)₀₋₆-C(=O)-N(R^{2d},R^{3d}); -(CH₂)₀₋₆-C(=NR^{2d})-N(R^{3d},R^{4d});
- (CH₂)₀₋₆-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d}); and a -(CH₂)₀₋₆-N(R^{3d}) group which is attached via the nitrogen atom to a carbon atom of a 5 to 6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a -(CH₂)₀₋₆- group attached to a 5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C₁₋₆-alkyl and C₁₋₆-alkylaryl, -CN; -NO₂; carbocyclic aryl, -CN; -NO₂; or

R^{2d} and R^{3d} taken together with the N atoms they are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

- 5 R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

J is a member selected from the group consisting of:

- 10 a direct link, -O-, -NH-, -NMe-, -C(=O)-NH-, -NH-C(=O)-;

X is a member selected from the group consisting of:

- (a) phenyl substituted with 0-3 R^{1e} groups;
- 15 (b) naphthyl substituted with 0-3 R^{1e} groups and
- (c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and
- 20 (d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

- 25 R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3 ; $-C_{1-4}$ -alkyl; carbocyclic aryl; $-C_{0-2}$ -alkyl-CN; $-O-R^{2e}$; $-C_{0-2}$ -alkyl-C(=O)-O- R^{2e} ; $-C_{0-2}$ -alkyl-C(=O)-N(R^{2e} , R^{3e}); $-C_{0-2}$ -alkyl-NO₂; $-C_{0-2}$ -alkyl-N(R^{2e} , R^{3e}); $-C_{0-2}$ -alkyl-SO₂-N(R^{2e} , R^{3e}); $-C_{0-2}$ -alkyl-SO₂- R^{2e} ; trihaloalkyl; $-O-C_{0-2}$ -alkyl-O- R^{2e} ; $-C_{0-2}$ -alkyl-O- R^{2e} ; $-O-C_{1-4}$ -alkyl-C(=O)-N(R^{2e} , R^{3e}); $-O-C_{1-4}$ -alkyl-C(=O)-O- R^{2e} ; $-C_{0-2}$ -alkyl-N(R^{2e})-C(=O)- R^{3e} ; $-C_{0-2}$ -alkyl-N(R^{2e})-SO₂- R^{3e} ; $-CH_2$ -N(R^{2e})-C(=O)- R^{3e} ; $-CH_2$ -N(R^{2e})-SO₂- R^{3e} ; $-(CH_2)_{0-6}$ -NR^{2e}R^{3e}; $-C(=O)$ -N(R^{2e} , R^{3e}); $-N(-(CH_2)_{1-6}-OR^{2e})_2$; $-N(R^{10})-(CH_2)_{1-6}-OR^{2e}$; $-N(R^{10})-C(=O)-R^{2e}$; $-N(R^{10})-SO_2-R^{2e}$; $-C(=N(R^{10}))$ -N(R^{2e} , R^{3e}); and a $-(CH_2)_{0-6}$ -5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

30

35

R^{10} , R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

5 H; $-C_{1-4}$ -alkyl; $-C_{0-2}$ -alkyl-O- R^{1g} ; $-C_{0-2}$ -alkyl-N($-R^{1g}$, $-R^{2g}$); $-C_{1-4}$ -alkyl-carbocyclic aryl; $-C_{1-4}$ -alkyl-heterocyclic; and R^{10} and R^{2e} , or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

10 R^{1g} and R^{2g} are independently a member selected from the group of:

H; halo; $-C_{1-4}$ -alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; $-CN$; $-C(=O)-N(R^{3g}, R^{4g})$; $-C(=O)-OR^{3g}$; $-NO_2$; $-(CH_2)_p-NR^{3g}R^{4g}$; $-SO_2NR^{3g}R^{4g}$; $-SO_2R^{3g}$; $-CF_3$; and $-(CH_2)_pOR^{3g}$;

15 p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4} -alkyl and $-C_{0-4}$ -alkyl-carbocyclic aryl;

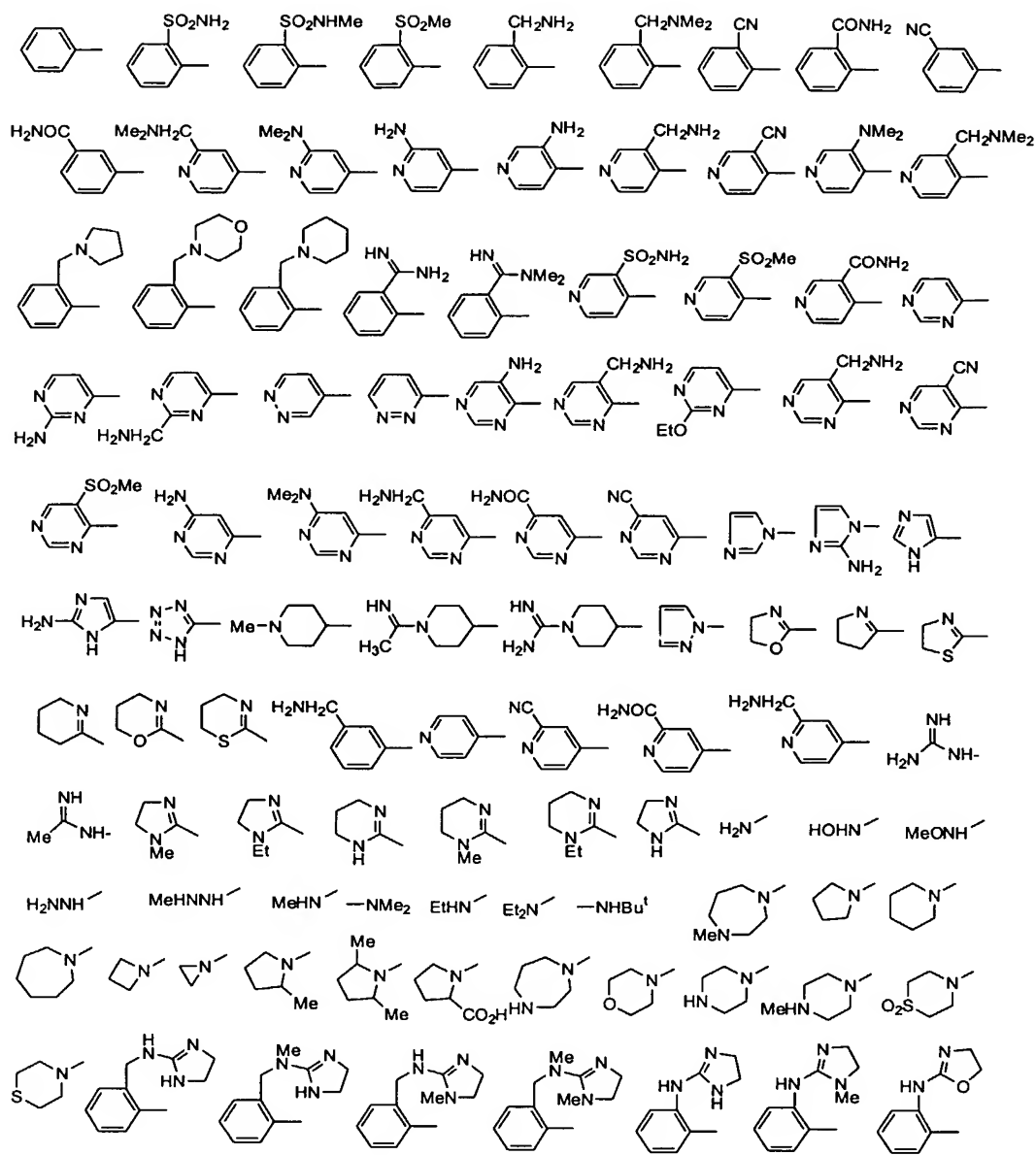
20 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In a still further preferred embodiment the present invention provides a compound according to the formula:

25 $A-Q-D-E-G-J-X$

wherein:

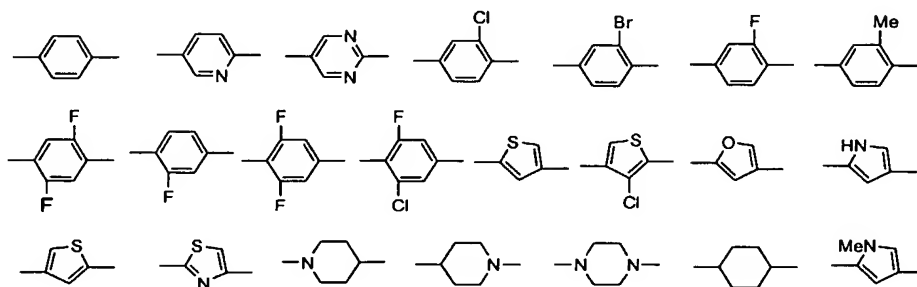
A is a member selected from the group consisting of:



Q is a member selected from the group consisting of:

a direct link, -C(=O)-, -NH-, -NMe-, -NHCH₂-, -NMeCH₂-, -C(=NH)-, -C(=NMe)-;

D is a direct link or is a member selected from the group consisting of:

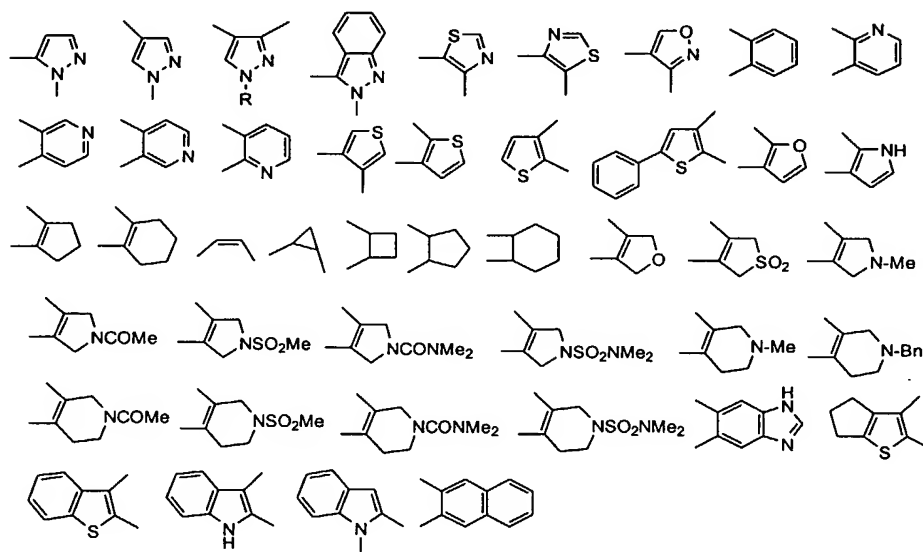


E is a member selected from the group consisting of:

a direct link, $-\text{CH}_2\text{NH}-$, $-\text{C}(=\text{O})-\text{NH}-$, $-\text{NH}-\text{C}(=\text{O})-$;

5

G is a member selected from the group consisting of:

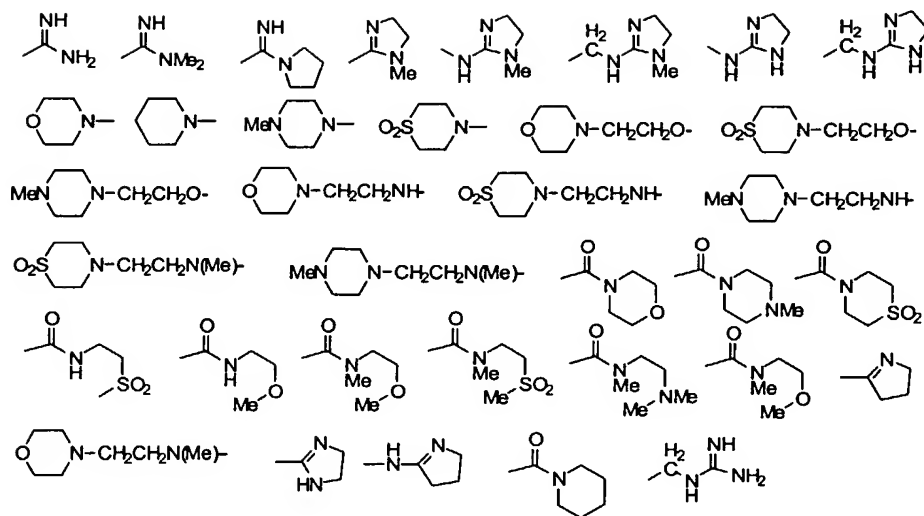


G is substituted by 0-4 R^{1d} groups and each R^{1d} group is independently selected from the group consisting of:

10

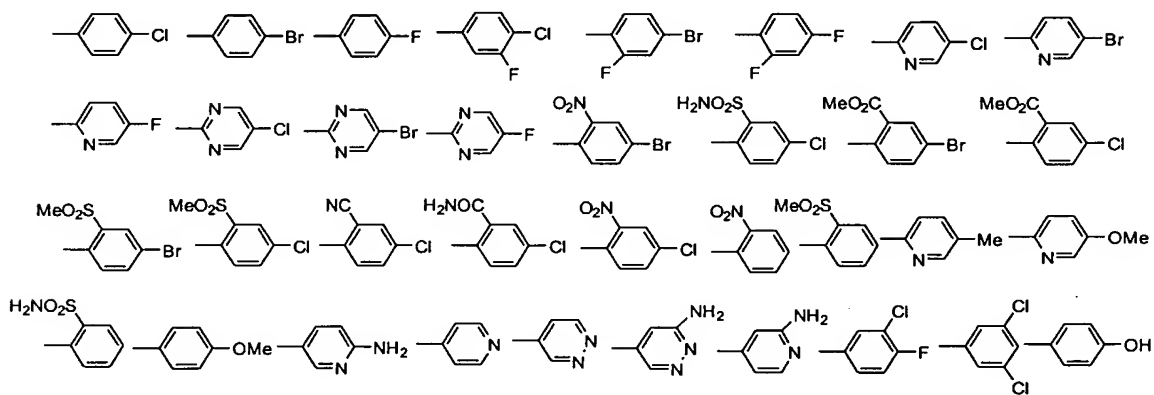
H, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{NH}_2$, $-\text{NMe}_2$, $-\text{OH}$, $-\text{OMe}$, $-\text{NHSO}_2\text{Me}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(=\text{O})-\text{OMe}$, $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{CH}_3$, $-\text{NHC}(=\text{O})\text{Me}$, $-\text{C}(=\text{O})\text{N}(-\text{Me})_2$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(-\text{Me})_2$, $-\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CO}_2\text{H}$, $-\text{OCH}_2\text{C}(=\text{O})-\text{OMe}$, $-\text{OCH}_2\text{C}(=\text{O})-\text{NH}_2$ and $-\text{OCH}_2\text{C}(=\text{O})\text{N}(-\text{Me})_2$.

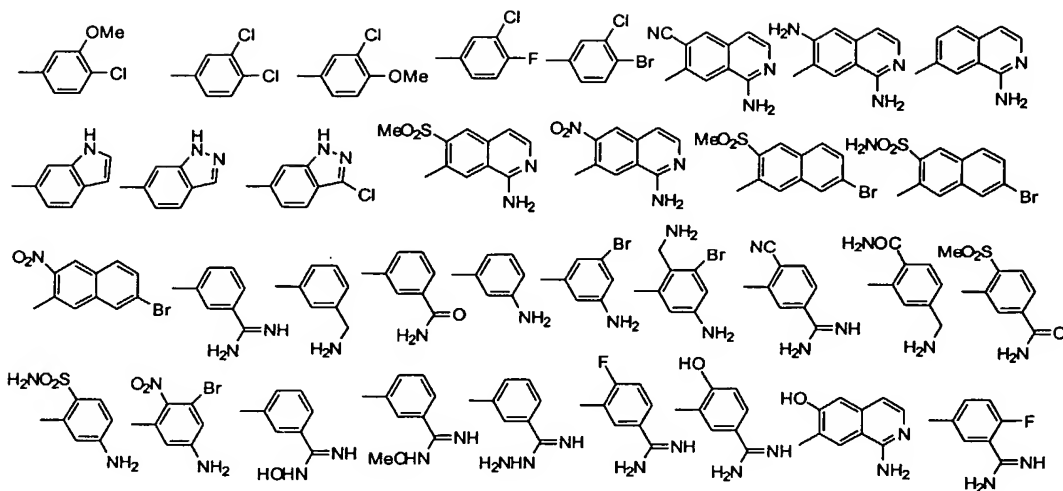
15



J is a member selected from the group consisting of:
a direct link, -O-, -NH-, -C(=O)-NH- and -NH-C(=O)-;

5 X is a member selected from the group consisting of:

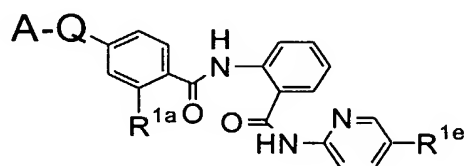




and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

5

In another further preferred embodiment the present invention provides a compound according to the formula:



wherein:

10 R^{1a} is a member selected from the group consisting of:

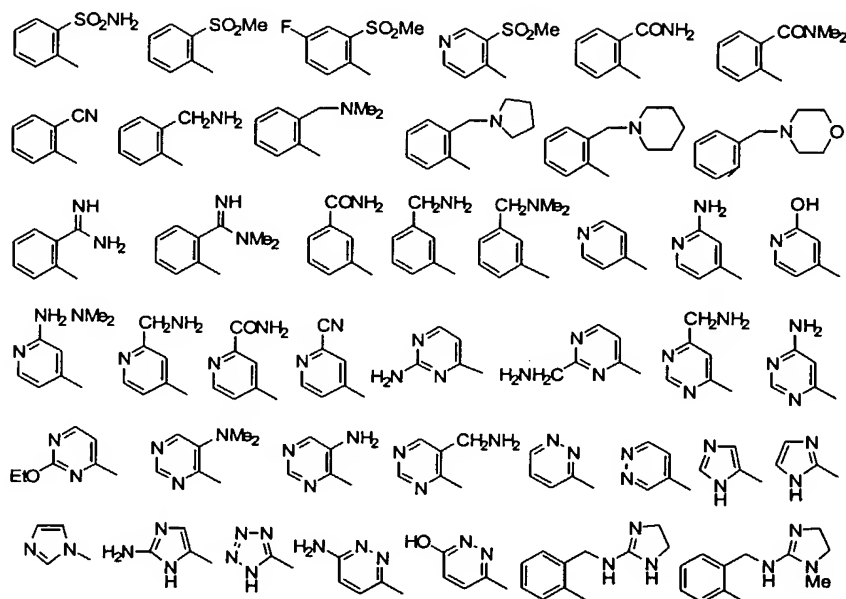
H, -F, -Cl and -Br;

R^{1e} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, -OH, -Me, -CF₃ and -CH₂NH₂; and

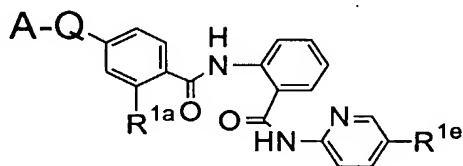
15

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and
5 prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:



10 wherein:

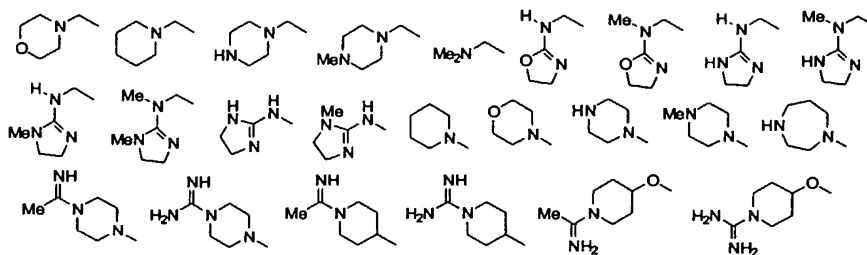
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and -Br;

R^{1c} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, -OH, -Me, -CF₃ and -CH₂NH₂; and

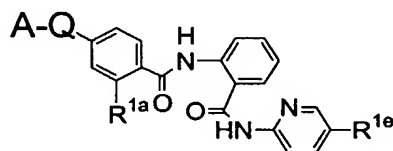
A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

5

In another further preferred embodiment the present invention provides a compound according to the formula:



10 wherein:

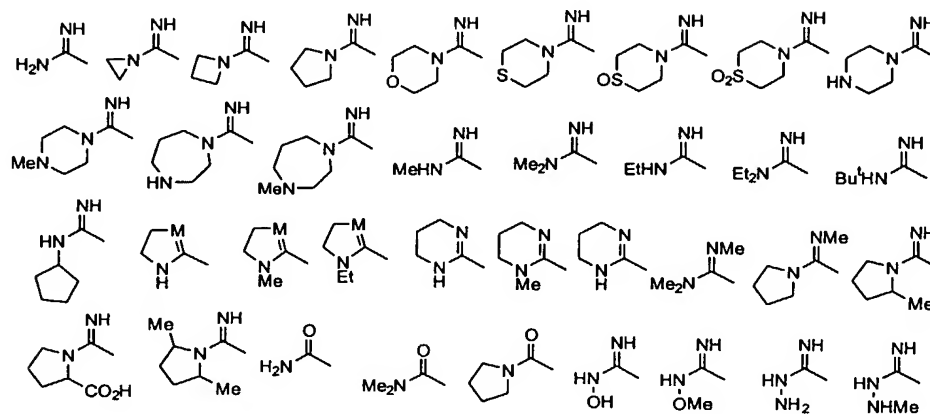
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and -Br;

R^{1e} is a member selected from the group consisting of:

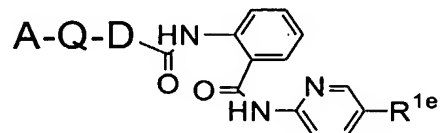
H, -F, -Cl, -Br, -OMe, -OH, -Me, -CF₃ and -CH₂NH₂;

A-Q is a member selected from the group consisting of:



5 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:



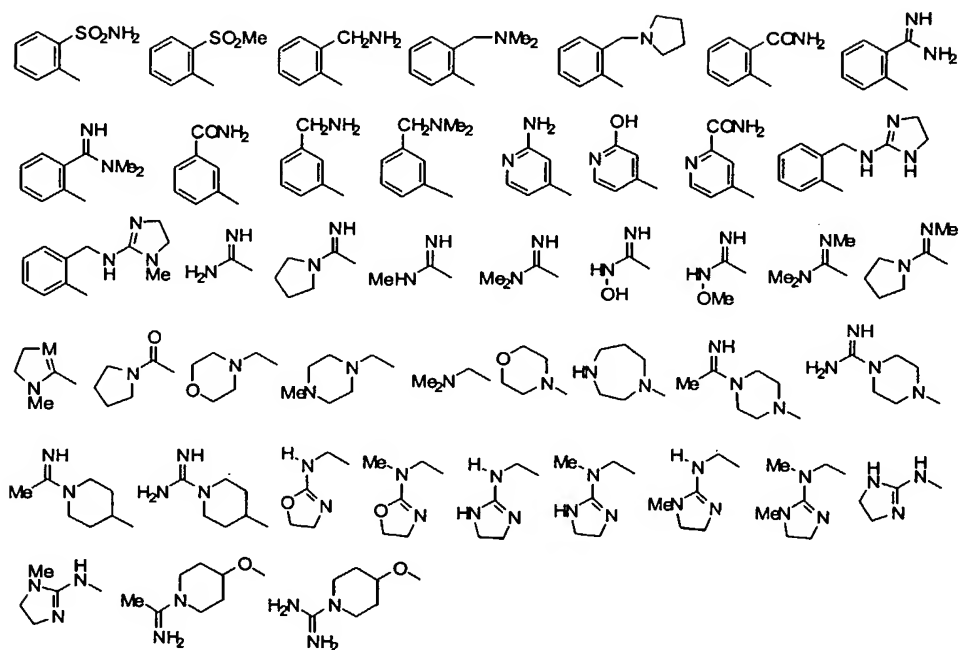
10 wherein:

R^{1e} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, -OH, -Me, -CF₃ and -CH₂NH₂;

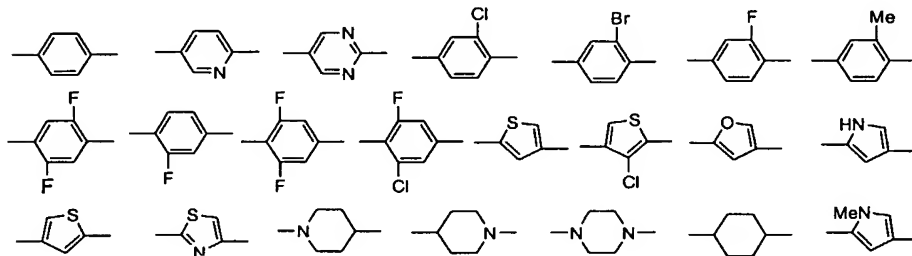
37

A-Q is a member selected from the group consisting of:



D is a member selected from the group consisting of:

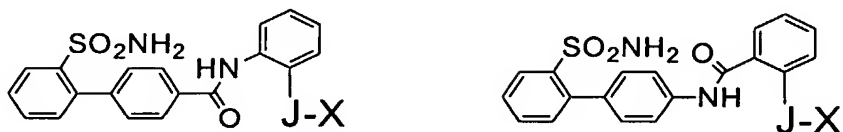
5



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

10

In another preferred embodiment the present invention provides a compound according to the formula:



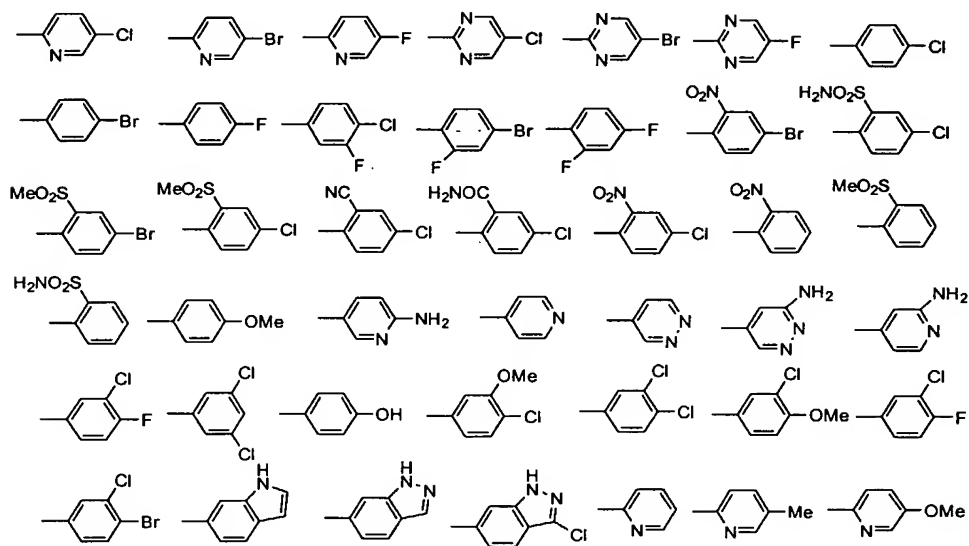
5 wherein:

J is a member selected from the group consisting of:

-NHC(=O)-, -C(=O)NH-;

X is a member selected from the group consisting of:

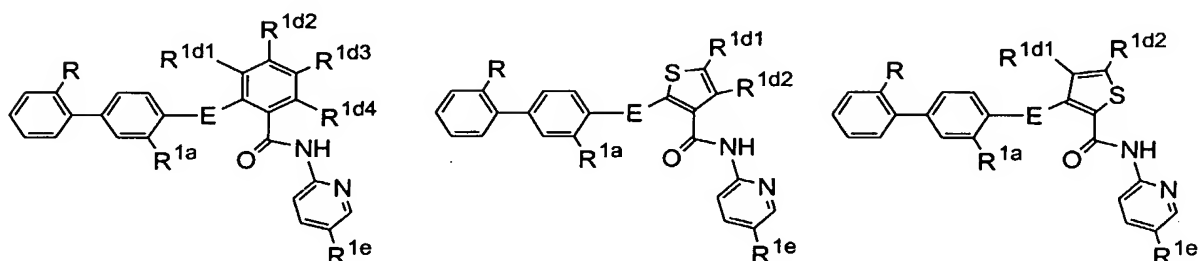
10



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

15

In another embodiment the present invention provides a compound according
 5 to the formula:



wherein:

R is a member selected from the group of :

-SO₂-NH₂ and -SO₂Me;

10

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

E is a member selected from the group consisting of:

15

-NHC(=O)- and -C(=O)NH-;

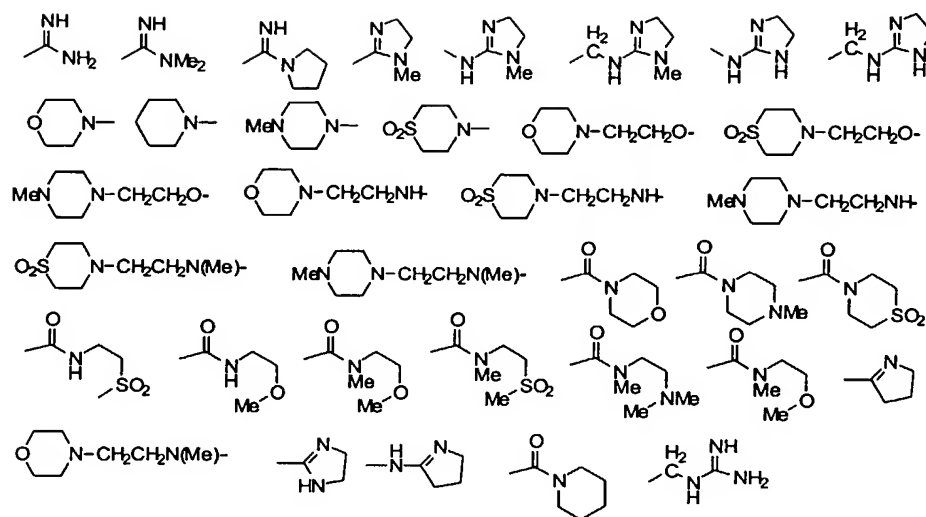
R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

H, -F, -Cl, -Br, -Me, -NO₂, -OH, -OMe, -NH₂, -NHAc, -NHSO₂Me, -CH₂OH
 and -CH₂NH₂;

20

R^{1d3} is a member selected from the group of:

H, -CH₃, -CF₃, -Cl, -F, -Br, -NH₂, -N(-Me)₂, -OH, -OMe, -NHSO₂Me, -NO₂,
 -CN, -C(=O)-OMe, -CO₂H, -C(=O)-NH₂, -SO₂NH₂, -SO₂CH₃, -NHC(=O)-Me,
 -C(=O)-N(-Me)₂, -CH₂NH₂, -CH₂-N(-Me)₂, -CH₂OH, -OCH₂CO₂H,
 25 -OCH₂C(=O)-OMe, -OCH₂C(=O)-NH₂, and -OCH₂C(=O)-N(-Me)₂.



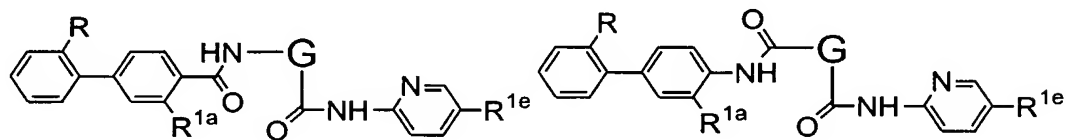
R^{1e} is a member selected from the group of :

F, -Cl, -Br, -OH, -Me and -Ome,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

5

In another further preferred embodiment the present invention provides a compound according to the formula:



10 wherein:

R is a member selected from the group consisting of:

-SO₂NH₂, -SO₂Me;

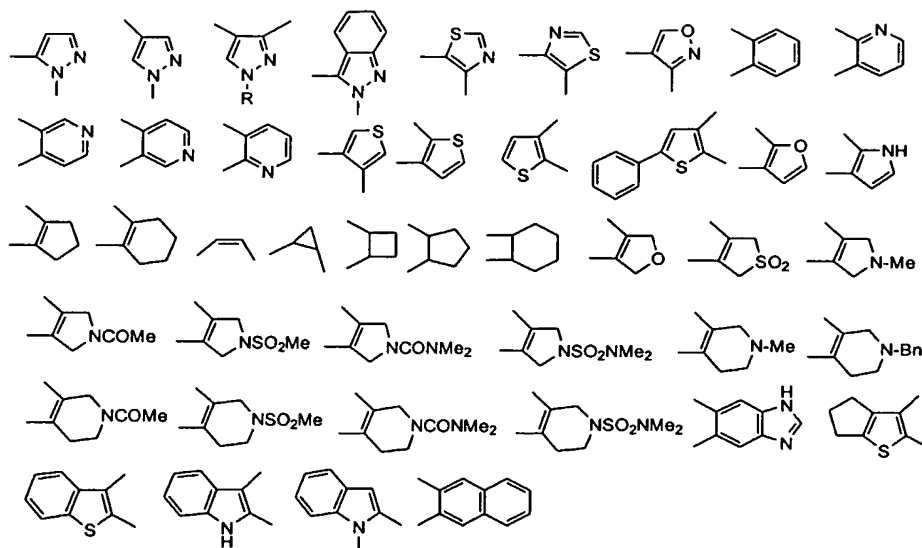
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and Br;

15 R^{1e} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, -OH, -Me, -CF₃ and -CH₂NH₂; and

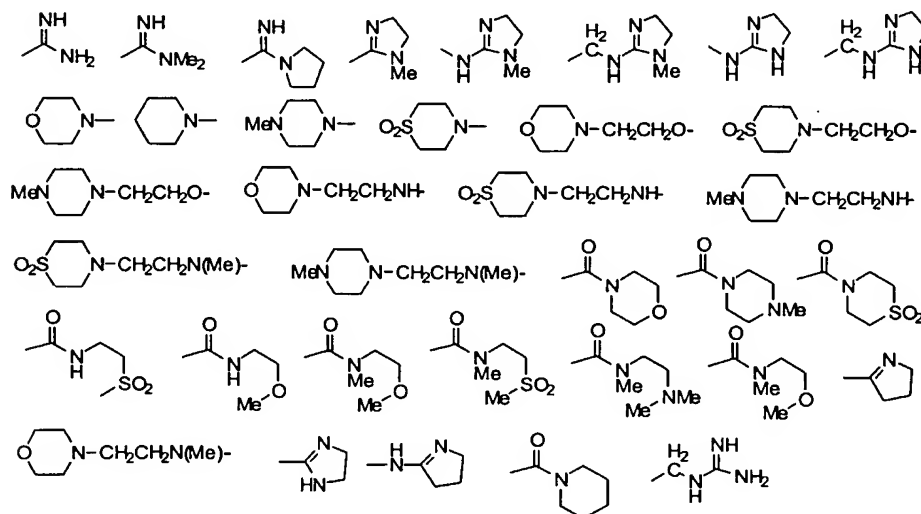
G is a member selected from the group consisting of:



wherein each G group may be substituted by 0-4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

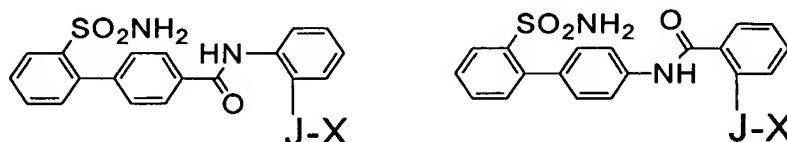
- 5 H, -CH₃, -CF₃, -Cl, -F, -Br, -NH₂, -N(-Me)₂, -OH, -OMe, -NHSO₂Me, -NO₂,
 -CN, -C(=O)-OMe, -CO₂H, -C(=O)-NH₂, -SO₂NH₂, -SO₂CH₃, -NH-C(=O)-Me,
 -C(=O)-N(-Me)₂, -CH₂NH₂, -CH₂-N(-Me)₂, -CH₂OH, -OCH₂CO₂H,
 -OCH₂CO₂Me, -OCH₂C(=O)-NH₂, -OCH₂C(=O)-N(-Me)₂

10



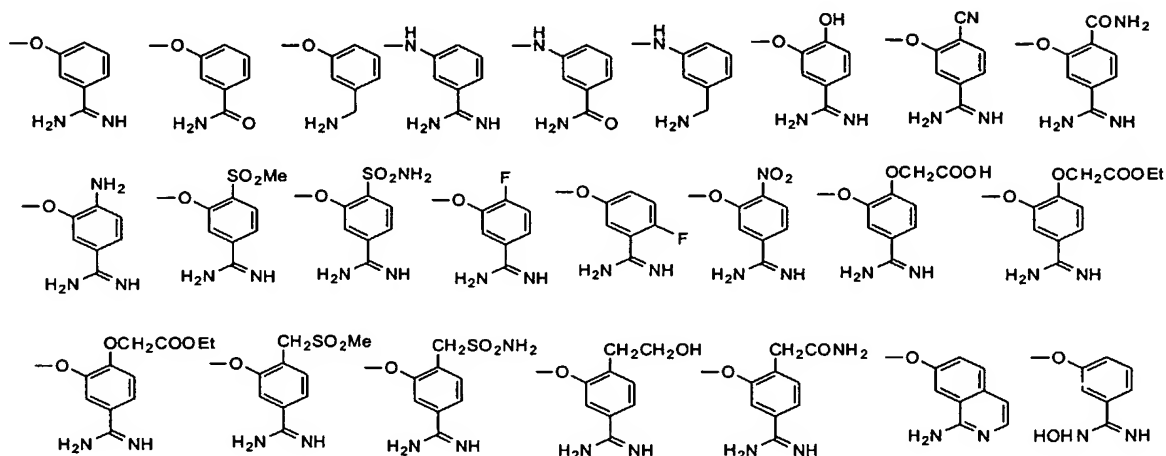
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

- 5 In another further preferred embodiment the present invention provides a compound according to the formula:



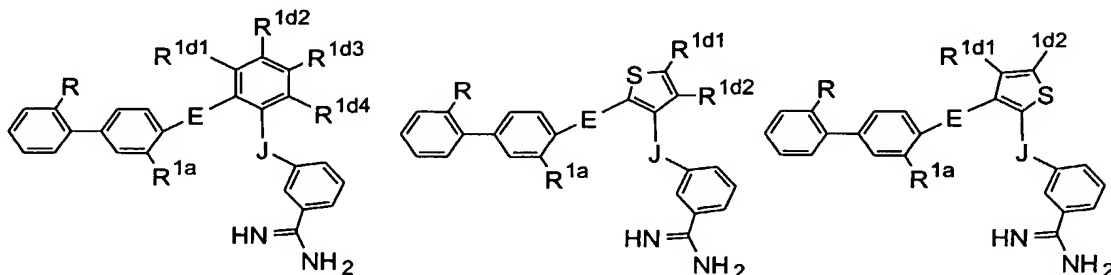
- 10 wherein:

J-X are collectively a member selected from the group consisting of:



- 15 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:



wherein:

- 5 R is a member selected from the group of :
-SO₂NH₂, and -SO₂Me;

R^{1a} is a member selected from the group of:
H, -F, -Cl and Br;

10

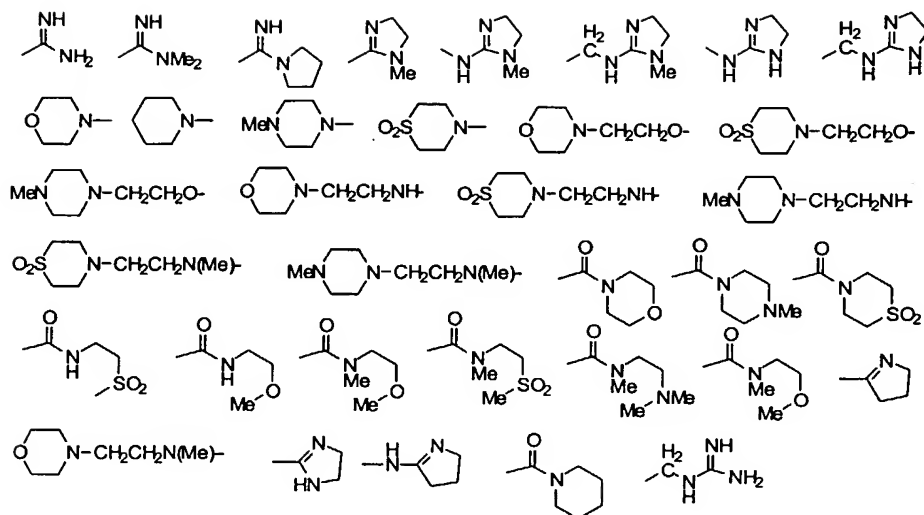
E is a member selected from the group consisting of:
-NHC(=O)- and -C(=O)NH-;

- J is a member selected from the group consisting of:
15 -NHC(=O)- and -C(=O)NH-, O;

R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:
H, -F, -Cl, -Br, -Me, -NO₂, -OH, -OMe, -NH₂, -NHAc, -NHSO₂Me, -CH₂OH,
-CH₂NH₂;

20

R^{1d3} is a member selected from the group of:
H, -CH₃, -CF₃, -Cl, -F, -Br, -NH₂, -N(-Me)₂, -OH, -OMe, -NHSO₂Me, -NO₂,
-CN, -CO₂Me, -CO₂H, -C(=O)-NH₂, -SO₂NH₂, -SO₂CH₃, -NHC(=O)-Me,
-C(=O)-N(-Me)₂, -CH₂NH₂, -CH₂-N(-Me)₂, -CH₂OH, -OCH₂CO₂H,
25 -OCH₂C(=O)-OMe, -OCH₂C(=O)-NH₂, -OCH₂C(=O)-N(-Me)₂.



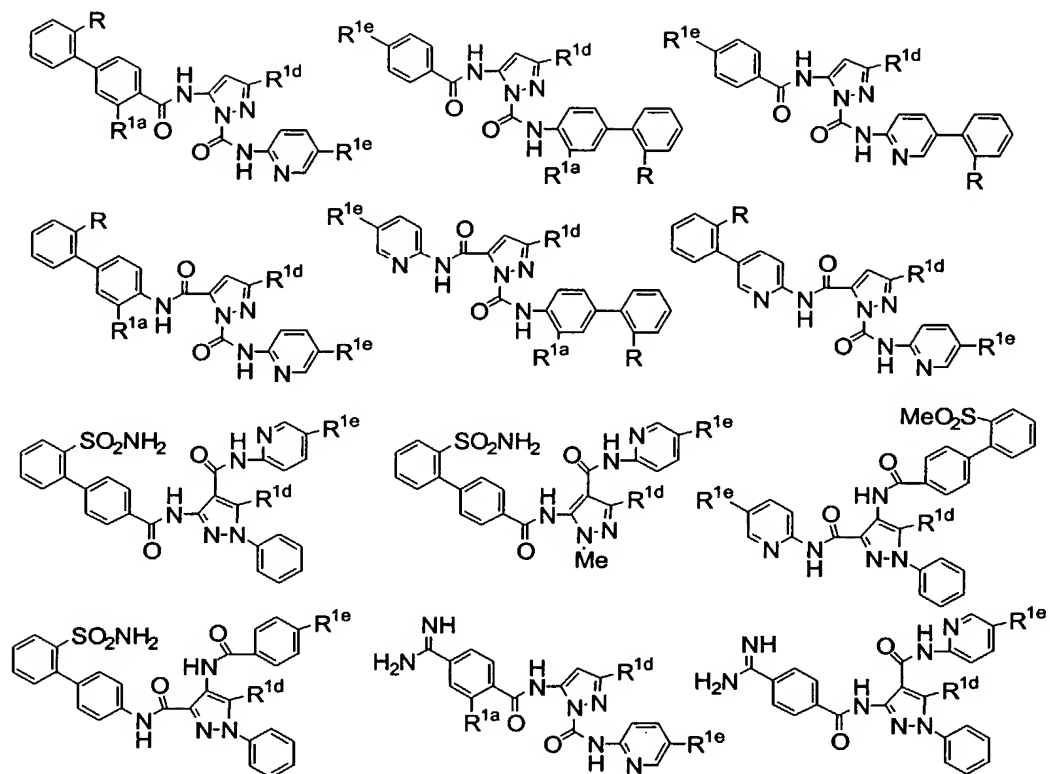
R^{1c} is a member selected from the group of :

F, -Cl, -Br, -OH, -Me and -OMe;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and

5 prodrug derivatives thereof.

In another preferred embodiment the present invention provides a compound of the following formulae, which illustrate the compounds having preferred substituents for G, particularly when G is a pyrazole ring structure.



wherein:

R is a member selected from the group of :

-SO₂-NH₂, and -SO₂Me;

5

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

R^{1d} is a member selected from the group consisting of:

-H, -CH₃, -CF₃, -CN, -SO₂NH₂ and -SO₂CH₃; and

10

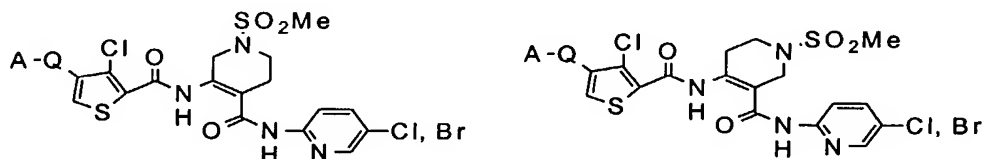
R^{1e} is a member selected from the group of:

-Cl and -Br;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

15

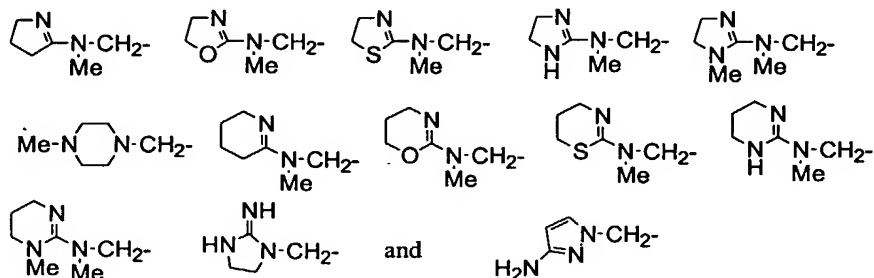
In another preferred embodiment the present invention provides a compound of the following formulae, which illustrate the compounds having preferred substituents for A-Q taken collectively when the remainder of the compound structure has the one of the following two formulae:



5

wherein:

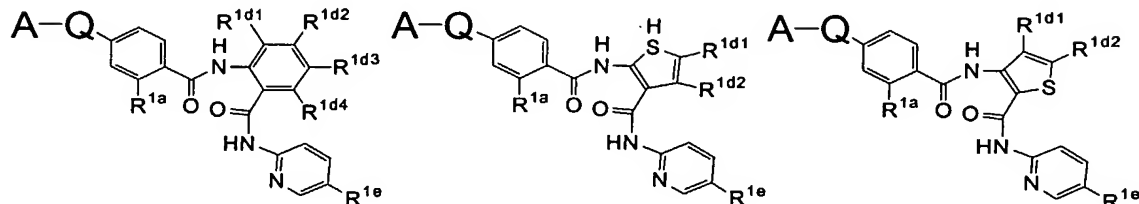
A-Q taken together are a member selected from the group consisting of:



10

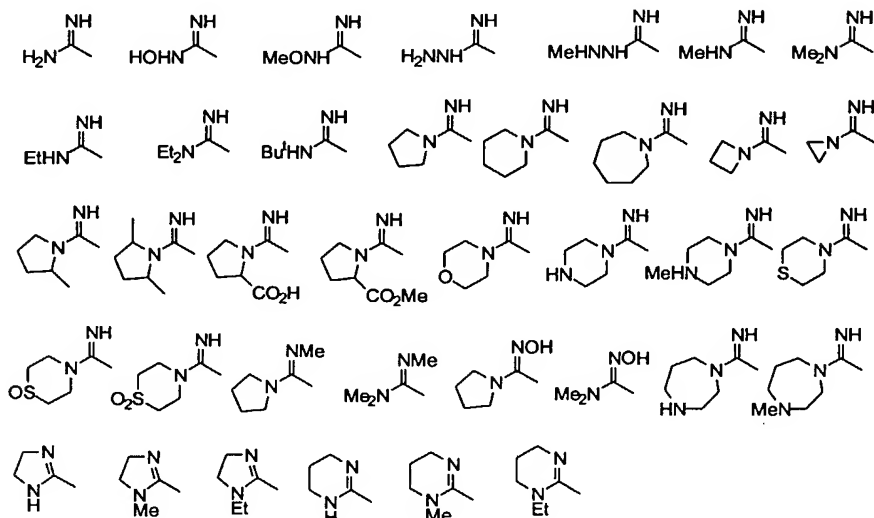
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another preferred embodiment the present invention provides a compound according to the formula:



wherein:

- 5 A-Q is a member selected from the group of :



R^{1a} is a member selected from the group of:

- 10 H, -F, -Cl and Br;

R^{1d1} , R^{1d2} , and R^{1d4} are independently a member selected from the group of:

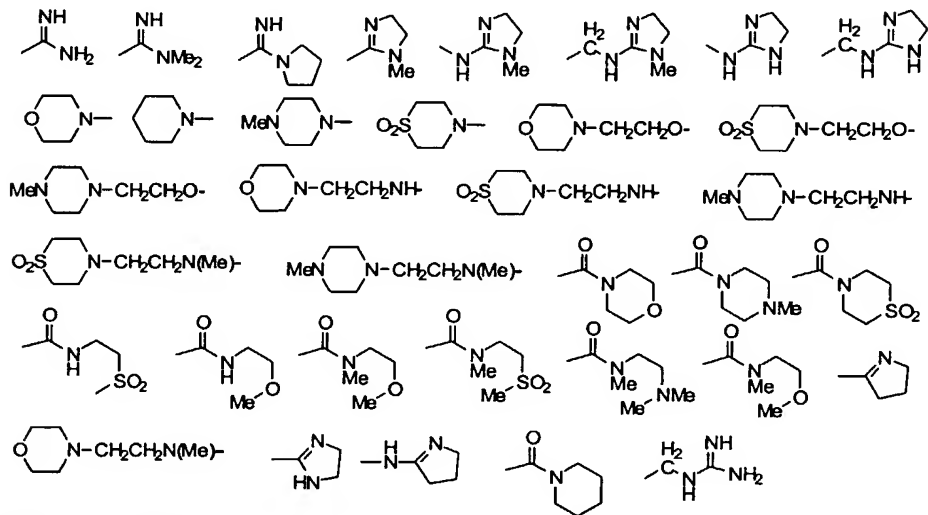
H, -F, -Cl, -Br, -Me, -NO₂, -OH, -OMe, -NH₂, -NHAc, -NHSO₂Me, -CH₂OH, -CH₂NH₂

- 15

R^{1d3} is a member selected from the group of:

H, -CH₃, -CF₃, -Cl, -F, -Br, -NH₂, -N(-Me)₂, -OH, -OMe, -NHSO₂Me, -NO₂,
-CN, -C(=O)-OMe, -CO₂H, -C(=O)-NH₂, -SO₂NH₂, -SO₂CH₃, -NHC(=O)-Me,

-C(=O)-N(Me)₂, -CH₂NH₂, -CH₂-N(-Me)₂, -CH₂OH, -OCH₂CO₂H, -OCH₂C(=O)-OMe, -OCH₂C(=O)-NH₂, -OCH₂C(=O)-N(-Me)₂,



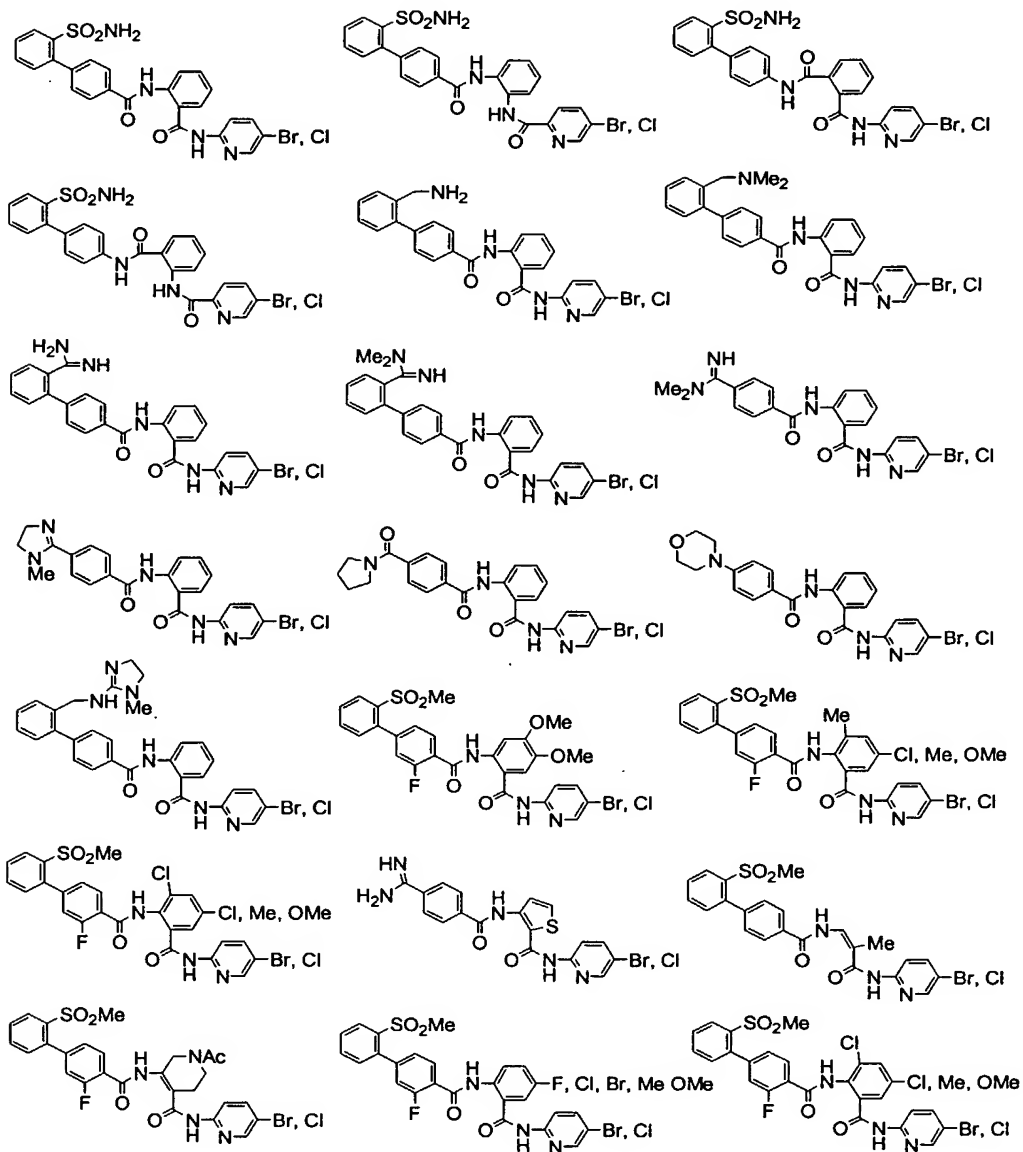
R^{1e} is a member selected from the group of:

5 F, -Cl, -Br, -OH, -Me and -OMe;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

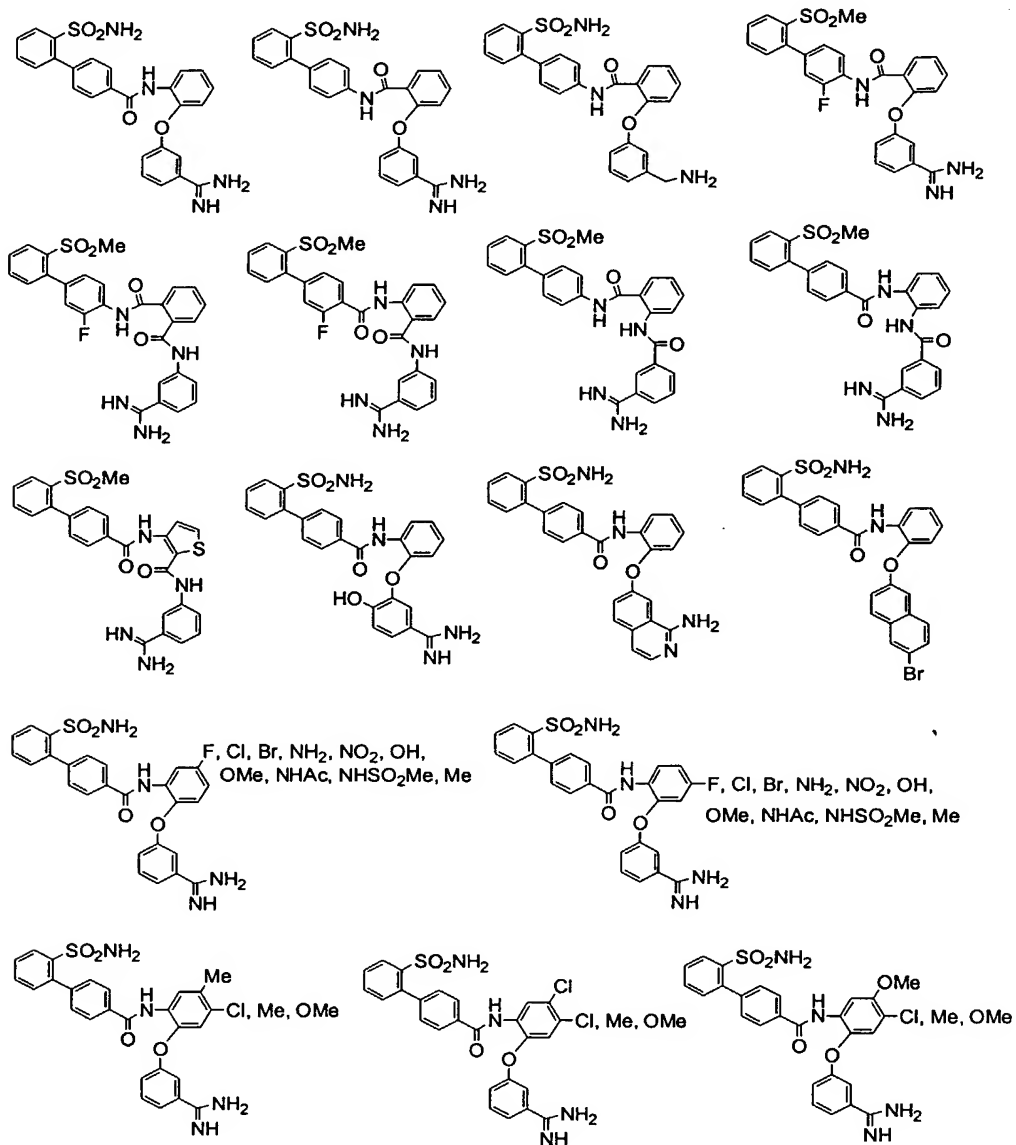
10

In another further preferred embodiment the present invention provides the following compounds:



5 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides the following compounds:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and
5 prodrug derivatives thereof.

This invention also encompasses all pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrug derivatives of the preferred compounds. In addition, the preferred compounds can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with

5 pharmaceutically acceptable salts, hydrates, solvates, and prodrug derivatives of such isomers and tautomers.

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are
10 within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described
15 above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or
20 base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Prodrug Derivatives of Compounds

25 This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups
30 cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the
35 organism, and indicating the number of functionalities present in a precursor-type

form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992).

5 Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other
10 features herein taught to enhance bioavailability.

As mentioned above, the compounds of this invention find utility as therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina,
15 myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these compounds are useful for the treatment or prophylaxis of those diseases which involve the
20 production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and prothrombotic states in which the coagulation cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

25 Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases treatable or preventable by the
30 administration of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in
35 the formation of life-threatening thrombi occurring throughout the microvasculature

leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

5 The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

10 The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the
15 present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side-effects. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals such as primates, (e.g.
20 humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy,
25 and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Diagnostic applications of the compounds of this invention will typically utilize formulations in the form of solutions or suspensions. In the management of
30 thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal
35 efficacy. The dose and method of administration will vary from subject to subject and

be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

5

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrans, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronic or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be 3-11, more preferably 5-9 and most preferably 7-8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as orally, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The

compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

5

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

10

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

25

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

30

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other

35

routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

10 The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg and more preferably about 1 to 20 mg/kg on a regimen in a single or 2 to 4 divided daily doses and/or continuous infusion.

15 Typically, about 5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

20 Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

35

Preparation of Compounds

The compounds of the present invention may be synthesized by either solid or liquid phase methods described and referenced in standard textbooks, or by a combination of both methods. These methods are well known in the art. See, 5 Bodanszky, "The Principles of Peptide Synthesis", Hafner, *et al.*, Eds., Springer-Verlag, Berlin, 1984.

Starting materials used in any of these methods are commercially available 10 from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where 15 otherwise indicated.

During the synthesis of these compounds, the functional groups of the amino acid derivatives used in these methods are protected by blocking groups to prevent cross reaction during the coupling procedure. Examples of suitable blocking groups 20 and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, *et al.*, Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

Compounds according to the invention can be synthesized utilizing procedures 25 well known in the art. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods.

Compositions and Formulations

30 The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

35

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Diagnostic applications of the compounds of this invention will typically utilize formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose

or its derivatives, glucose, mannose or dextrans, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

5 Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be
10 between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously,
15 intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as
20 biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar
25 vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties,
30 to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this
35 invention may be coupled to a class of biodegradable polymers useful in achieving

controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

- 5 Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial
10 having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of
15 therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology.
20 Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels
25 being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this
30 invention may be administered several times daily, and other dosage regimens may also be useful.

Typically, about 0.5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is
35 compounded with a physiologically acceptable vehicle, carrier, excipient, binder,

preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

5 Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above
10 materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty
15 vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

 In practicing the methods of this invention, the compounds of this invention
20 may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet
25 aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

30 The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous
35 vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also
5 characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower
10 extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both
15 vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

The compounds of this present invention, selected and used as disclosed
20 herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically
25 mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous thrombosis or pulmonary embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated
30 intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications associated with extracorporeal
35 circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation

procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

5

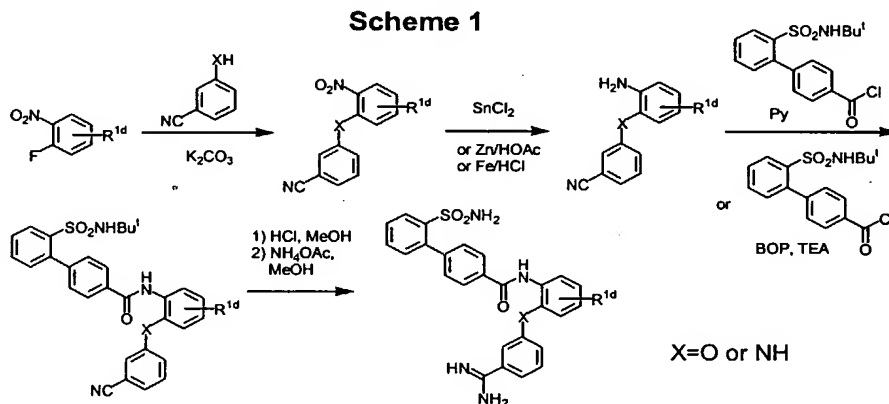
Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods.

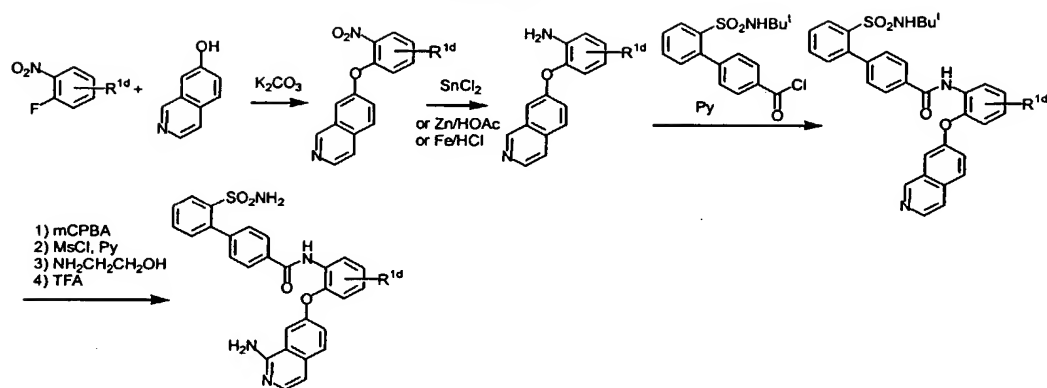
EXAMPLES

Examples of Chemical Production Process General Reaction Schemes

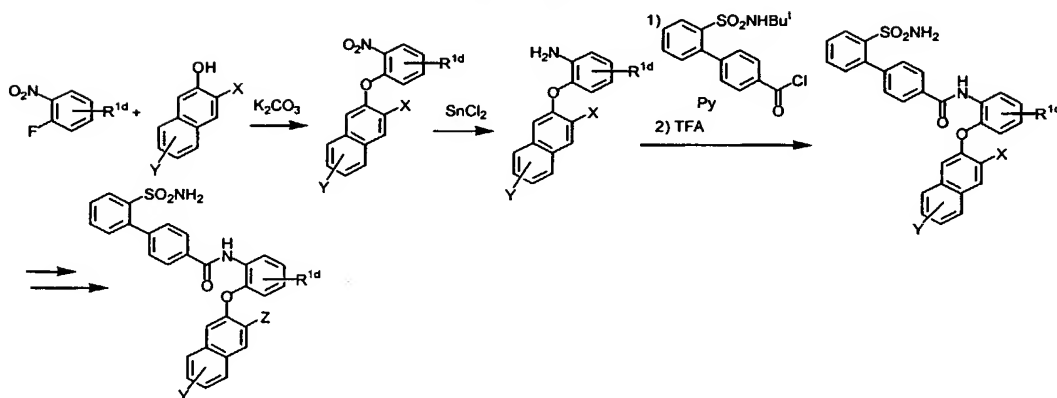
20



Scheme 2

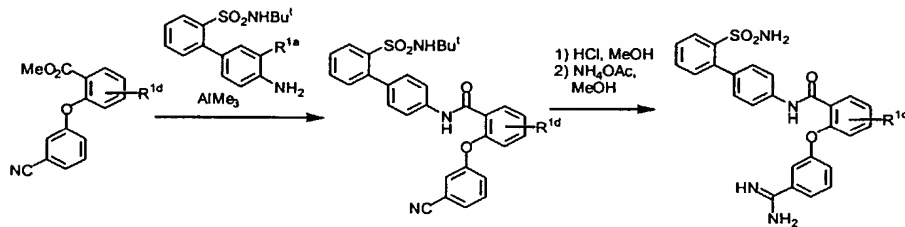


Scheme 3

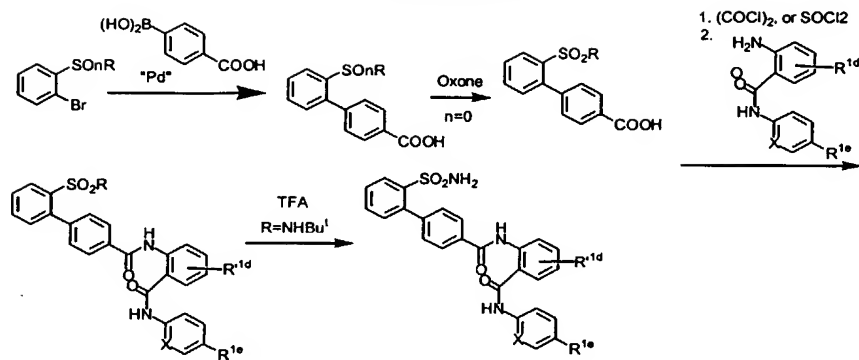


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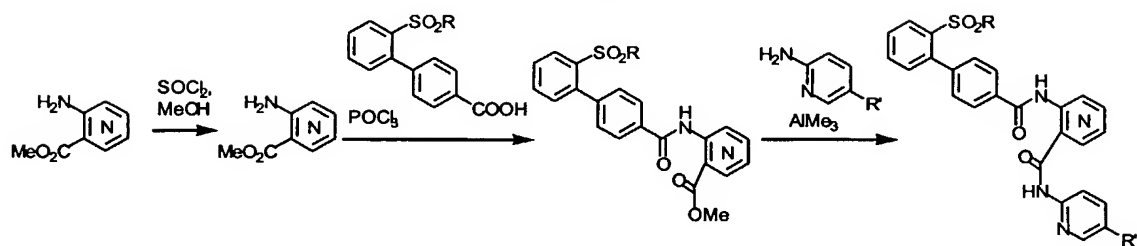
Scheme 4



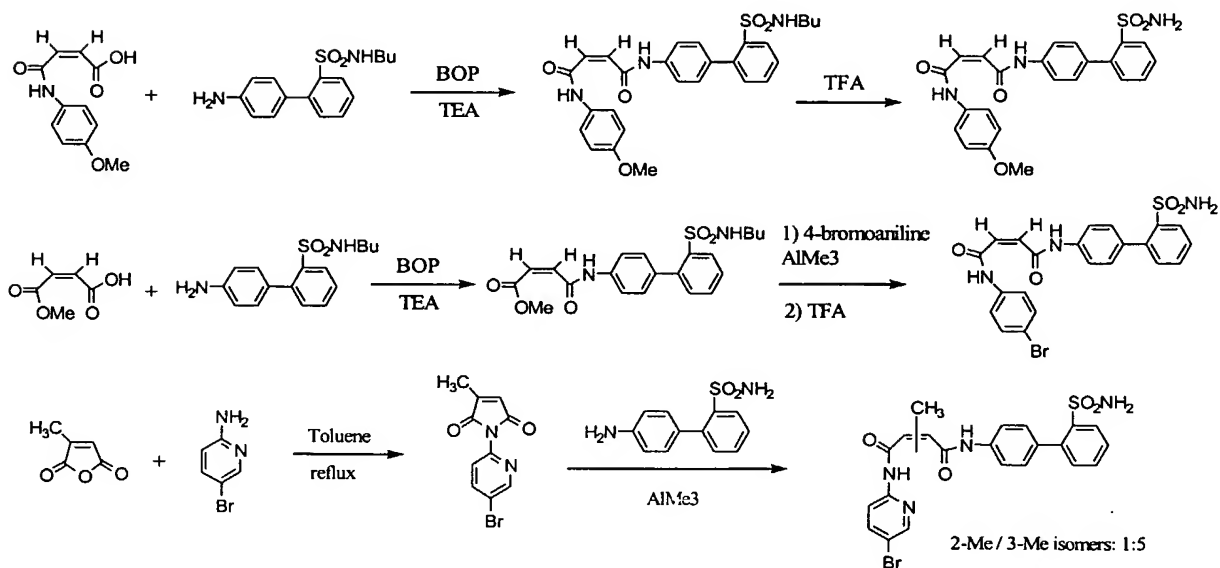
Scheme 5



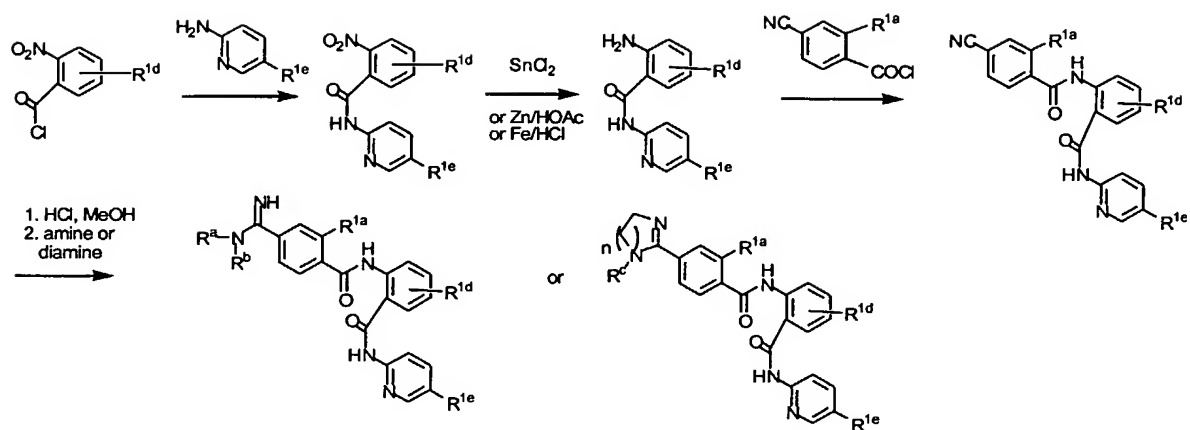
Scheme 6



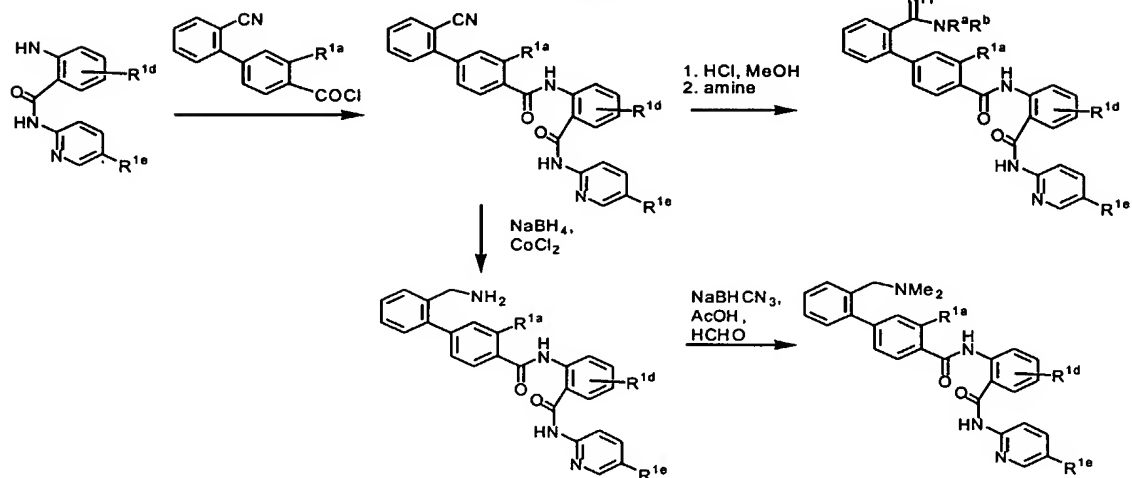
Scheme 7



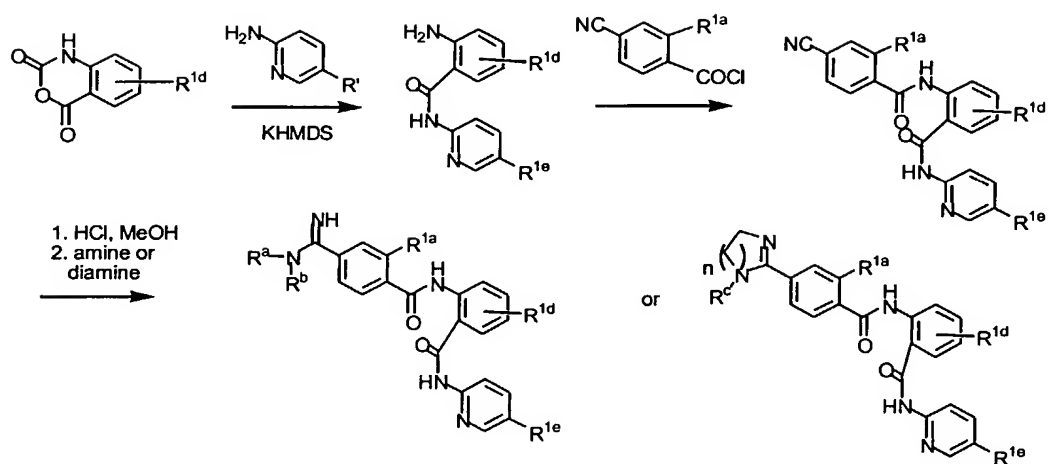
Scheme 8



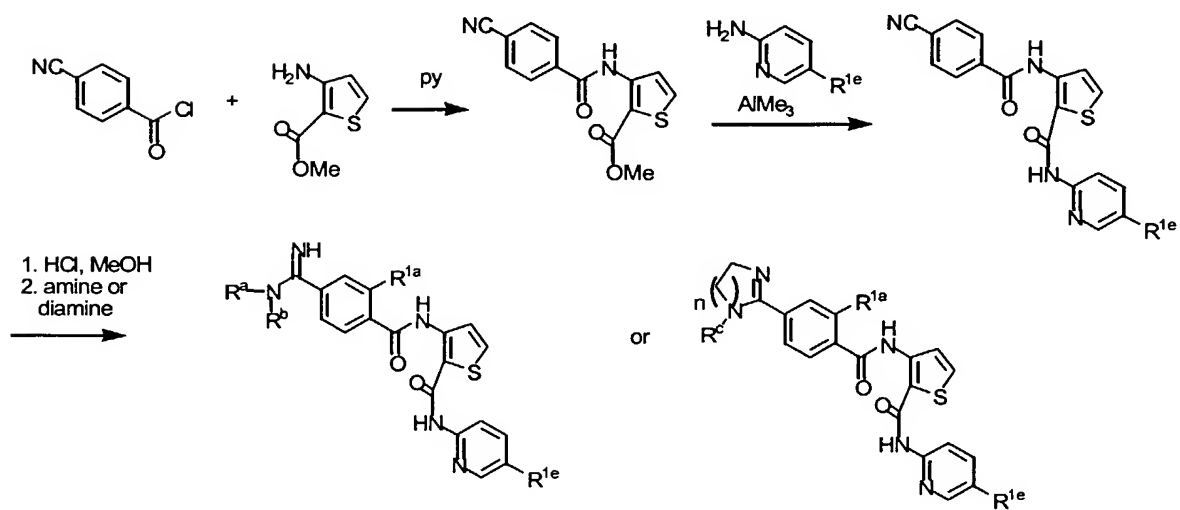
Scheme 9



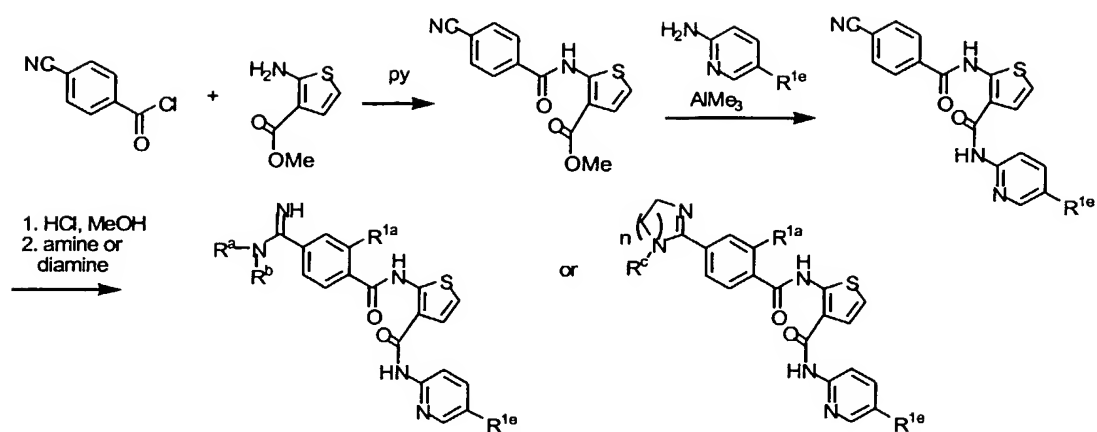
Scheme 10



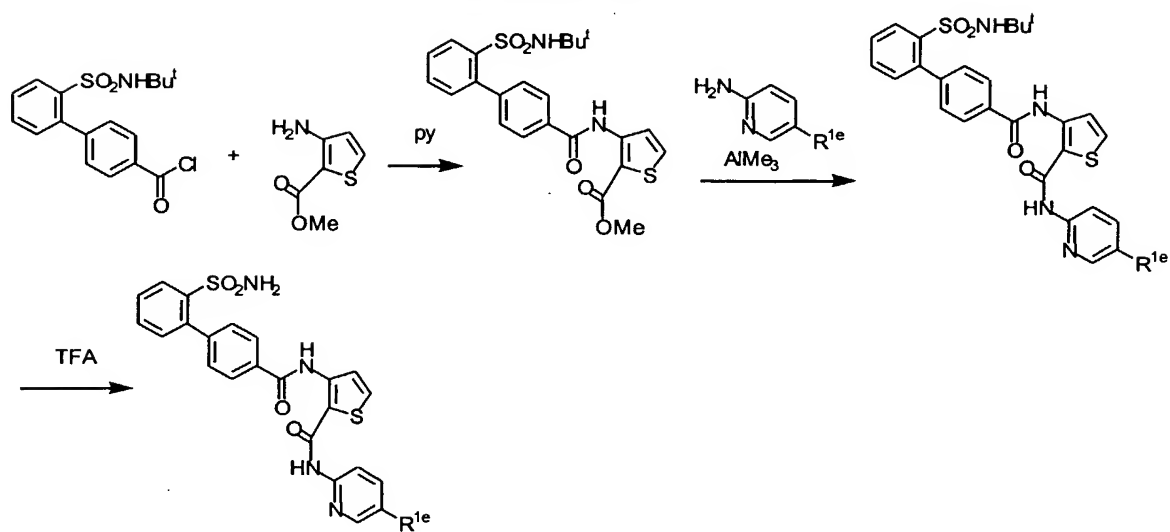
Scheme 11



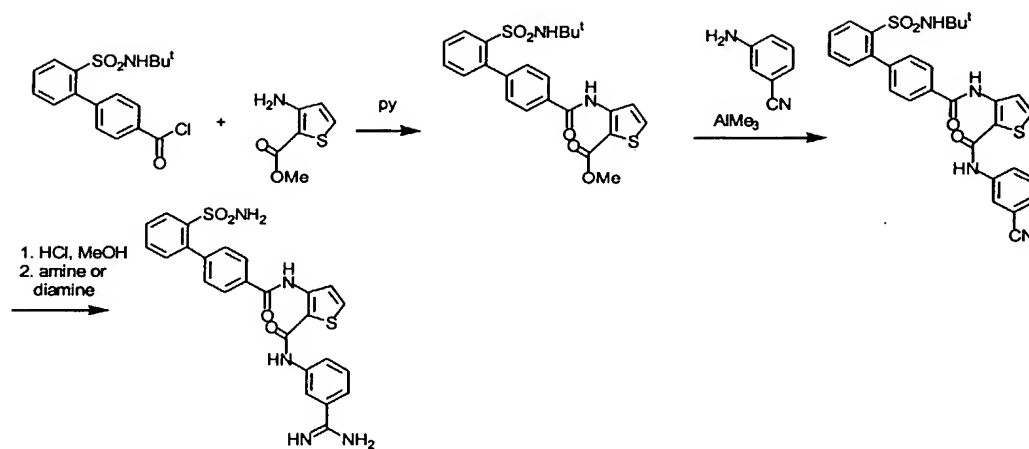
Scheme 12



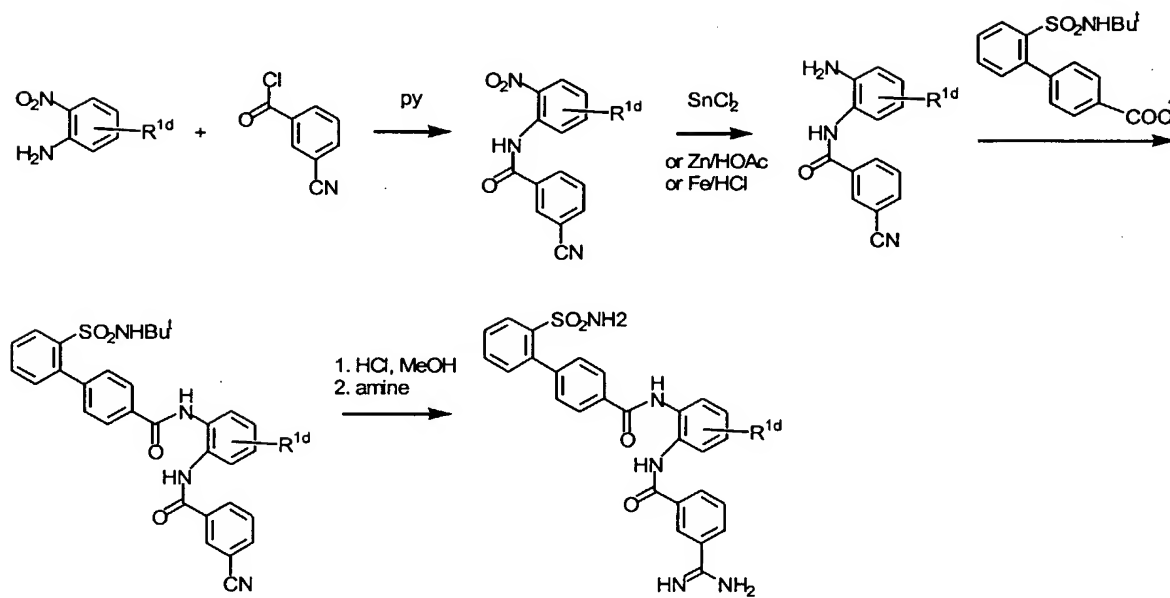
Scheme 13

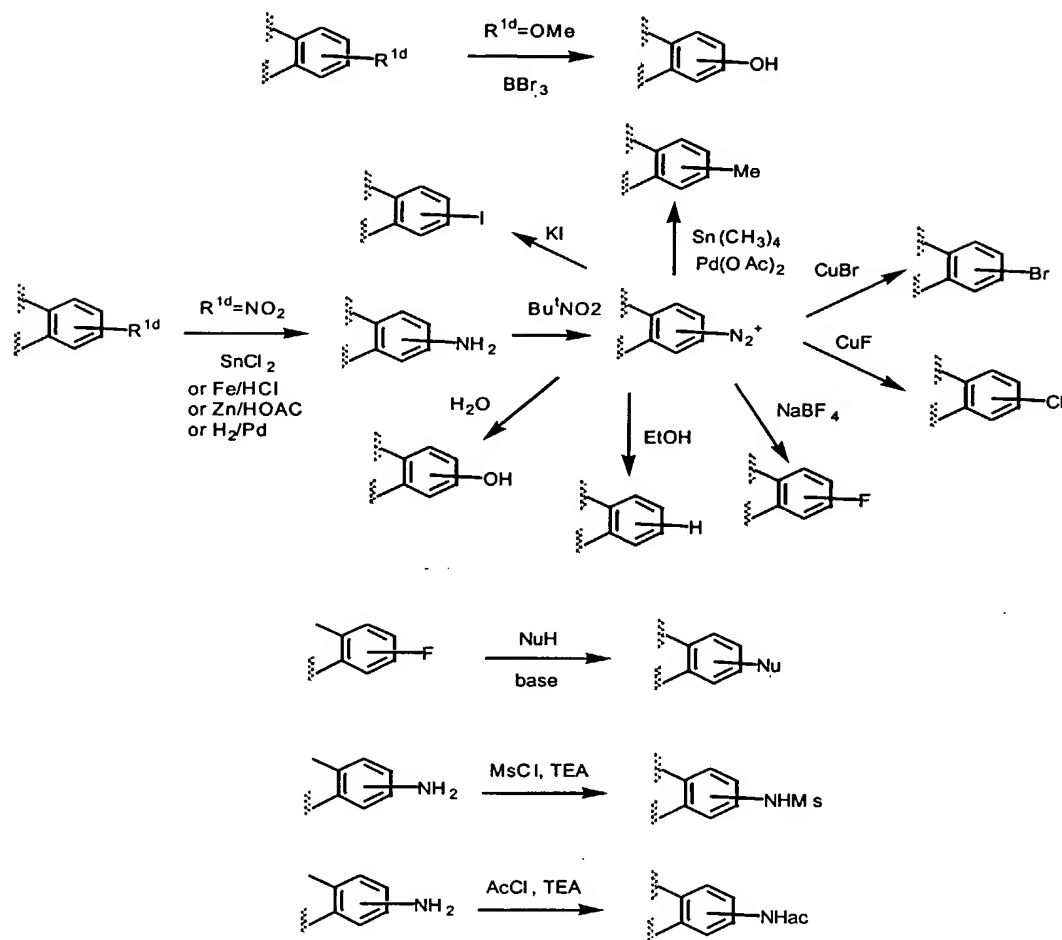


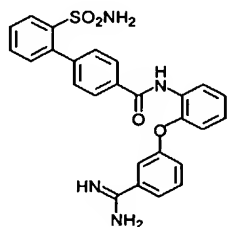
Scheme 14



Scheme 15



Scheme 16: Transformations of R^{1d}

Example 1**3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)phenoxy)benzamidine.**

- 5 Step 1: To a solution of 2-fluoro nitrobenzene (1.41 g, 10 mmol, 1.0 equiv) and 3-hydroxybenzonitrile (1.19 g, 1.0 equiv) in 10 mL of DMF was added K_2CO_3 (2.76 g, 2 equiv). After stirring at 60°C for 3 h, the mixture was diluted with EtOAc and washed with H_2O . The organic layer was dried over $MgSO_4$, filtered and evaporated to give 3-(2-nitrophenoxy)benzonitrile (2.38 g, 99%). MS found for $C_{13}H_9N_2O_3$ (M+H)⁺: 241.

10

Step 2: A solution of 3-(2-nitrophenoxy)benzonitrile (1.21 g, 5 mmol, 1.0 equiv) in 30 mL of EtOH was treated with $SnCl_2 \cdot 2H_2O$ (3.38 g, 3 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$,
 15 filtered and evaporated to give 3-(2-aminophenoxy)benzonitrile (1.04 g, 99%). MS found for $C_{13}H_{11}N_2O$ (M+H)⁺: 211.

- Step 3: A mixture of 3-(2-aminophenoxy)benzonitrile (210 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880
 20 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O . The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy)benzonitrile (300 mg, 57%). MS found for $C_{30}H_{28}N_3O_4S$ (M+H)⁺: 526.

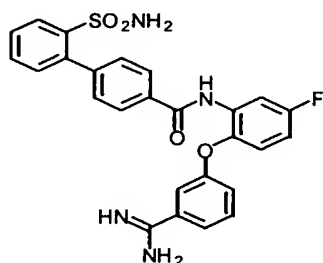
25

Step 4: A stream of HCl(g) was bubbled through a 0°C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy)benzonitrile (53 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5

equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give 3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzamidine (40 mg, 83%). MS found for C₂₆H₂₃N₄O₄S (M+H)⁺: 487.

Example 2

3-(4-fluoro-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy)benzamidine.

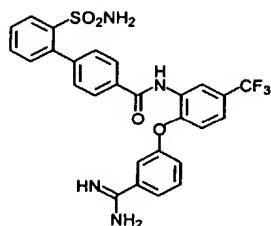


Step 1: A mixture of 3-(2-amino-4-fluorophenoxy)benzonitrile (230mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-fluoro-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (495 mg, 91%). MS found for C₃₀H₂₇FN₃O₄S (M+H)⁺: 544.

Step 2: A stream of HCl(g) was bubbled through a 0°C solution of 3-(4-fluoro-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (55 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give 3-(4-fluoro-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (39 mg, 77%). MS found for C₂₆H₂₂FN₄O₄S (M+H)⁺: 505.

Example 3

3-(4-trifluoromethyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.

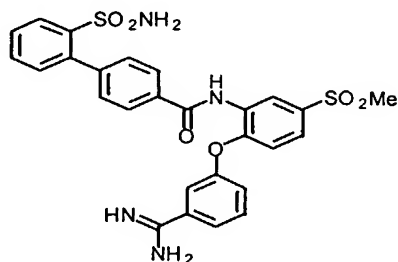


- 5 Step 1: A mixture of 3-(2-amino-4-trifluoromethylphenoxy)benzonitrile (280 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-trifluoromethyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (529 mg, 89%). MS found for C₃₁H₂₇F₃N₃O₄S (M+H)⁺: 594.

- Step 2: A stream of HCl(g) was bubbled through a 0°C solution of 3-(4-trifluoromethyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (59 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give 3-(4-trifluoromethyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (35 mg, 63%). MS found for C₂₇H₂₂F₃N₄O₄S (M+H)⁺: 555.

Example 4

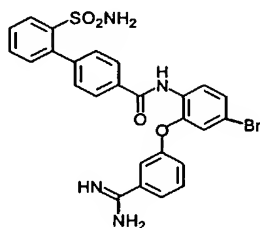
- 3-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.**



- Step 1: A mixture of 3-(2-amino-4-methylsulfonylphenoxy)benzonitrile (290 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (429 mg, 71%). MS found for C₃₁H₃₀N₃O₆S₂ (M+H)⁺: 604.
- Step 2: A stream of HCl(g) was bubbled through a 0°C solution of 3-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (60 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give 3-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (27 mg, 47%). MS found for C₂₇H₂₅N₄O₆S₂ (M+H)⁺: 565.

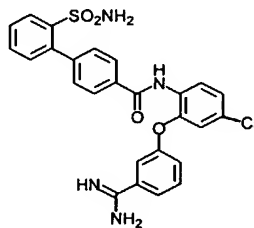
20 Examples 5-8

The following compounds of Examples 5-8 were prepared using the procedure described in Example 1:



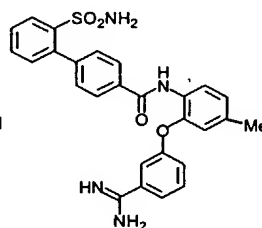
Example 5

MS (M+H):
565



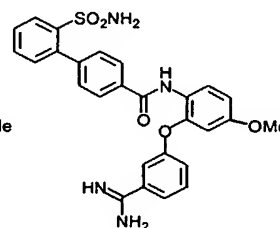
Example 6

MS (M+H):
521



Example 7

MS (M+H):
501

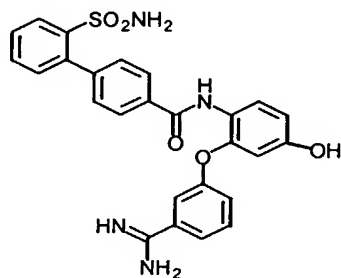


Example 8

MS (M+H):
517

Example 9

3-(5-hydroxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.

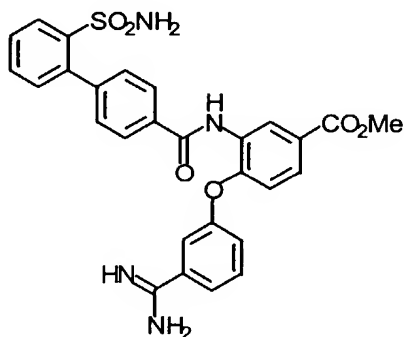


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Step 1: A solution of 3-(5-methoxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino) phenoxy) benzamidine (52 mg, 0.1 mmol, 1 equiv) in 5 mL of methylene chloride was treated with BBr₃ (1 M in dichloromethane, 0.5 mL, 5 equiv) overnight. The reaction was quenched with water carefully and after the volatile was evaporated, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give 3-(5-hydroxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine. (41 mg, 82%). MS found for C₂₆H₂₃N₄O₆S (M+H)⁺: 503.

15 **Example 10**

3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.



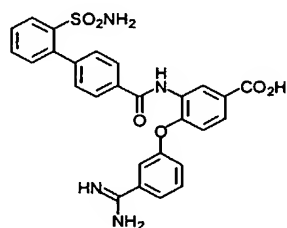
20

Step 1: A mixture of 3-(2-amino-4-methoxycarbonylphenoxy)benzonitrile (270 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-methoxycarbonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (502 mg, 86%). MS found for C₃₂H₃₀N₃O₆S (M+H)⁺: 584.

Step 2: A stream of HCl(g) was bubbled through a 0°C solution of 3-(4-methoxycarbonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (58 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (29.5 mg, 54%). MS found for C₂₈H₂₅N₄O₆S (M+H)⁺: 545.

Example 11

3-(4-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.



A solution of 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (10.9 mg, 0.02 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h.

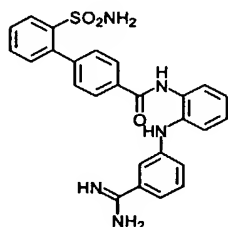
Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H₂O/CH₃CN to give 3-(4-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (8.9 mg, 84%). MS found for C₂₇H₂₃N₄O₆S (M+H)⁺: 531.

5

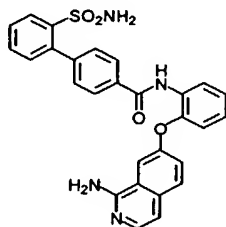
Example 12

3-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylamino) benzamidine.

10



- Step 1: A mixture of 3-(2-amino-phenylamino)benzonitrile (196 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered and evaporated. Flash chromatography on silica gel gave 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino) phenylamino) benzonitrile (226 mg, 43%). MS found for C₃₀H₂₉N₄O₃S (M+H)⁺: 525.
- Step 2: A stream of HCl(g) was bubbled through a 0°C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenylamino) benzonitrile (53 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylamino) benzamidine (27 mg, 55%). MS found for C₂₆H₂₄N₅O₃S (M+H)⁺: 486.

Example 13**7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)phenoxy)-1-aminoisoquinoline.**

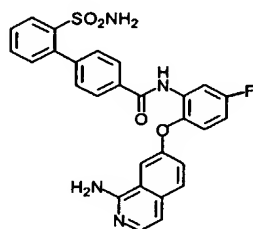
- 5 Step 1: A mixture of 7-(2-aminophenoxy)isoquinoline (237 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H₂O. The organic layer was dried over MgSO₄, filtered and evaporated. Flash chromatography on silica gel
10 gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy) isoquinoline (469 mg, 85%). MS found for C₃₂H₃₀N₃O₄S (M+H)⁺: 552.

- Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy) isoquinoline (110 mg, 0.2 mmol,
15 1 equiv) in 5 mL of acetone was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partitioned between methylene chloride and saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄ and used in the next step directly.

- 20 Step 3: The compound obtained in step 2 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyridine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over MgSO₄, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After
25 removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)phenoxy)-1-aminoisoquinoline (43 mg, 42%). MS found for C₂₈H₂₃N₄O₄S (M+H)⁺: 511.

Example 14**7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy)1-aminoisoquinoline.**

5



Step 1: A mixture of 7-(2-amino-4-fluorophenoxy)isoquinoline (255 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H₂O. The organic layer was dried over MgSO₄, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy) isoquinoline (467 mg, 82%). MS found for C₃₂H₂₉FN₃O₄S (M+H)⁺: 570.

Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy) isoquinoline (114, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partitioned between methylene chloride and saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄ and used in the next step directly.

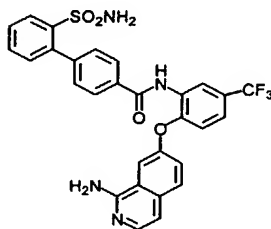
Step 3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyridine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over MgSO₄, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-

4-fluorophenoxy)1-aminoisoquinoline (77 mg, 50%). MS found for $C_{28}H_{22}FN_4O_4S$ (M+H)⁺: 529.

Example 15

5

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy)1-aminoisoquinoline.



- 10 Step 1: A mixture of 7-(2-amino-4-trifluoromethylphenoxy)isoquinoline (305 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H₂O. The organic layer was dried over MgSO₄, filtered and evaporated. Flash chromatography
- 15 on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy) isoquinoline (360 mg, 58%). MS found for $C_{33}H_{29}F_3N_3O_4S$ (M+H)⁺: 620.

- Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy) isoquinoline (124 mg, 0.2 mmol, 1 equiv) in 5 mL of acetone
- 20 was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partitioned between methylene chloride and saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄ and used in the next step directly.

25

- Step3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyridine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over MgSO₄,
- 30 filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After

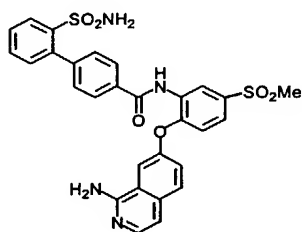
removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy)1-aminoisoquinoline (64 mg, 52%). MS found for C₂₉H₂₂F₃N₄O₄S (M+H)⁺: 579.

5

Example 16

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy)1-aminoisoquinoline.

10



Step 1: A mixture of 7-(2-amino-4-methylsulfonylphenoxy)isoquinoline (315 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H₂O. The organic layer was dried over MgSO₄, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy) isoquinoline (460 mg, 73%). MS found for C₃₃H₃₂N₃O₆S₂ (M+H)⁺: 630.

20

Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy) isoquinoline (126 mg, 0.2mmol, 1 equiv) in 5 mL of acetone was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partitioned between methylene chloride and saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄ and used in the next step directly.

25

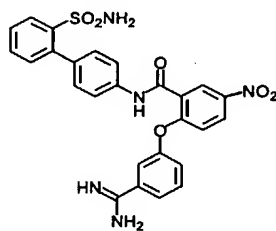
Step 3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyridine was removed under reduced

- pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over MgSO_4 , filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with
- 5 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy)1-aminoisoquinoline (94 mg, 80%). MS found for $\text{C}_{29}\text{H}_{25}\text{N}_4\text{O}_6\text{S}_2$ ($\text{M}+\text{H}$)⁺: 589.

Example 17

10

3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy)benzamidine.



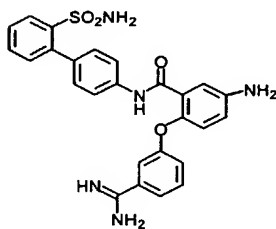
- 15 Step 1: A solution of 2-fluoro-5-nitrobenzoic acid (1.85 g, 10 mmol, 1.33 equiv) in thionyl chloride (5 mL) was refluxed for 2 h and evaporated. The residue was redissolved in 20 mL of methylene chloride and to the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]aniline (2.0 g, 1.0 equiv) and 5 mL of pyridine. After stirring at rt overnight, the volatile was evaporated. Flash chromatography on silica
- 20 gel 1-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl)-2-fluoro-5-nitrobenzene (2.9 g, 99%). MS found for $\text{C}_{23}\text{H}_{23}\text{FN}_3\text{O}_5\text{S}$ ($\text{M}+\text{H}$)⁺: 472.

- Step 2: To a solution of 1-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl)-2-fluoro-5-nitrobenzene (1.18 g, 0.25 mmol, 1.0 equiv) and 3-hydroxybenzonitrile (298 mg, 1.0 equiv) in 10 mL of DMF was added K_2CO_3 (691 mg, 2 equiv). After
- 25 stirring at 60°C for 3 h, the mixture was diluted with EtOAc and washed with H_2O . The organic layer was dried over MgSO_4 , filtered, evaporated and chromatographed to give 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (950 g, 63%). MS found for $\text{C}_{30}\text{H}_{27}\text{N}_4\text{O}_6\text{S}$ ($\text{M}+\text{H}$)⁺: 571.

Step 3: A stream of HCl(g) was bubbled through a 0°C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (57 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt
5 overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine (24 mg,
10 45%). MS found for C₂₆H₂₂N₅O₆S (M+H)⁺: 532.

Example 18

3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzamidine.
15

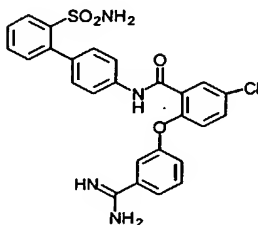


A mixture of 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine (53 mg, 0.1 mmol, 1 equiv), 5 mL of 1N HCl, 5 mg of Pd/C (10%) in 10
20 mL of methanol was stirred at rt under 1 atm H₂ atmosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzamidine (31 mg, 66%). MS found for C₂₆H₂₄N₅O₄S (M+H)⁺: 502.

25

Example 19**3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy)benzamidine.**

5



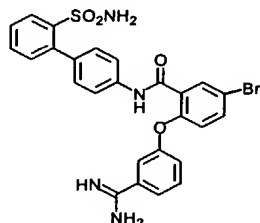
Step 1: A mixture of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (570 mg, 1 mmol, 1 equiv) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (677 mg, 3 equiv) in 25 mL of EtOAc was refluxed for 2 h. The reaction was quenched with sat. NaHCO_3 . The organic layer was separated and dried over MgSO_4 , filtered and evaporated to give 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzonitrile (45 mg, 83%). MS found for $\text{C}_{30}\text{H}_{29}\text{N}_4\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 541.

Step 2: A mixture of t-BuNO₂ (21 mg, 0.1 mmol, 2 equiv), CuCl (20 mg, 2 equiv) in 5 mL of acetonitrile was refluxed for 10 min. To the solution was added 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzonitrile (54 mg, 0.1 mmol, 1 equiv). The mixture was refluxed for 1h and evaporated. Flash chromatography with 1:2 EtOAc/hexane to give [(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzonitrile (43 mg, 77%) MS found for $\text{C}_{30}\text{H}_{27}\text{ClN}_3\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 561.

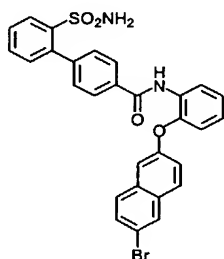
Step 3: A stream of HCl(g) was bubbled through a 0°C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzonitrile (56 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (40 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzamidine (47 mg, 84%). MS found for $\text{C}_{26}\text{H}_{22}\text{ClN}_4\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 521.

Example 20**3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-bromophenoxy)benzamidine.**

5



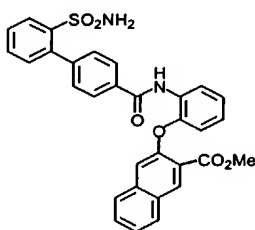
This compound is prepared according to the procedure described in example 19. MS found for $C_{26}H_{22}BrN_4O_4S$ (M+H)⁺: 565.

10 Example 21**2-bromo-6-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.**

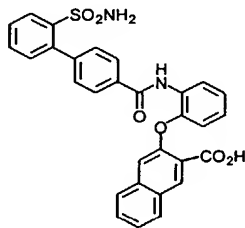
15

A mixture of 2-bromo-6-(2-aminophenoxy) naphthalene (314 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN gave 2-bromo-6-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (378 mg, 66%). MS found for $C_{29}H_{22}BrN_2O_4S$ (M+H)⁺: 573.

20

Example 22**3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.**

A mixture of 3-methoxycarbonyl-2-(2-aminophenoxy) (294 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN gave 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (420 mg, 76%). MS found for C₃₁H₂₅N₂O₆S (M+H)⁺: 553.

Example 23**3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.**

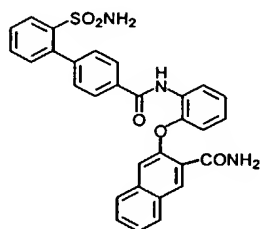
A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (55 mg, 0.1 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h.

Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H₂O/CH₃CN to give 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (47 mg, 88%). MS found for C₃₀H₂₃N₂O₆S (M+H)⁺: 539.

5

Example 24

3-aminocarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.



10

Step 1: A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (40 mg, 0.066 mmol) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, and acidified with 1N HCl until PH ~ 1-2. The product (39 mg, 100%), 3-hydroxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene, was extracted with EtOAc, dried over MgSO₄, filtered and evaporated. MS found for C₃₄H₃₁N₂O₆S (M+H)⁺: 595.

15

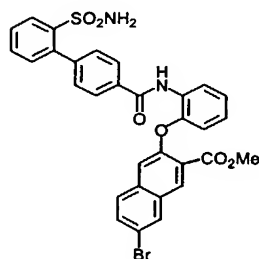
Step 2: A solution of 3-hydroxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (39 mg, 0.066 mmol) was refluxed in 3 mL of thionyl chloride for 2 h and evaporated. The residue was then stirred in 5 mL of 2M ammonia in methanol overnight. The volatile was evaporated and the residue was refluxed in 2 mL of trifluoroacetic acid overnight to give the product 3-aminocarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (14 mg, 39%) after HPLC (C18 reversed phase, eluting with 0.5% TFA in H₂O/CH₃CN). MS found for C₃₀H₂₄N₃O₅S (M+H)⁺: 538.

25

Example 25

3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene.

5



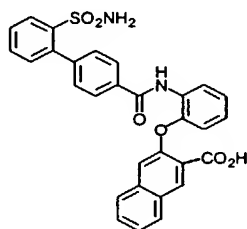
A mixture of 2-(2-aminophenoxy)-3-methoxycarbonyl-6-bromo naphthalene (372 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN gave 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene (423 mg, 67%). MS found for C₃₁H₂₄BrN₂O₆S (M+H)⁺: 631.

15

Example 26

3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene.

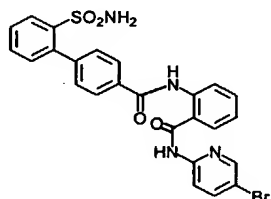
20



- A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy)-6-bromo naphthalene (63 mg, 0.1 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H₂O/CH₃CN to give 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene (47 mg, 78%). MS found for C₃₀H₂₂BrN₂O₆S (M+H)⁺: 617.

Example 27

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide.



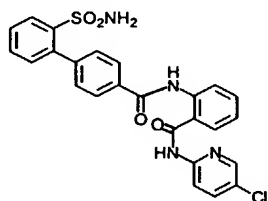
- Step 1: A solution of 2-nitrobenzoyl chloride (3.70 g, 20 mmol, 1.0 equiv), 2-amino-5-bromopyridine (3.50 g, 1.0 equiv), pyridine (10 mL) in 25 mL of methylene chloride was stirred overnight. The volatile was evaporated, flash chromatography on silica gel gave N-(5-bromo-2-pyridinyl)-(2-nitro)phenylcarboxamide (5.02 g, 77%). MS found for C₁₂H₉BrN₃O₃ (M+H)⁺: 322.
- Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro)phenylcarboxamide (1.0 g, 3.1 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with SnCl₂·2H₂O (2.80 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous NaHCO₃ and 1N NaOH. The organic layer was dried over MgSO₄, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (0.89 g, 98%). MS found for C₁₂H₁₁BrN₃O (M+H)⁺: 292.
- Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight,

washed with H₂O. The organic layer was dried over MgSO₄, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-

- 5 aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide (470 mg, 85%). MS found for C₂₅H₂₀BrN₄O₄S (M+H)⁺: 551.

Example 28

- 10 **N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide.**

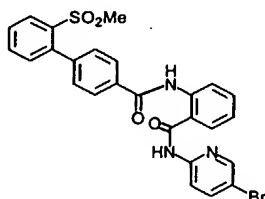


- A mixture of N-(5-chloro-2-pyridinyl)-(2-amino)phenylcarboxamide (247 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-
- 20 aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide (370 mg, 73%). MS found for C₂₅H₂₀ClN₄O₄S (M+H)⁺: 507.

Example 29

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.

5



Step 1: To a mixture of 2-bromothioanisole (4.8g, 23.6mmol), 4-carboxybenzeneboronic acid (3.92g, 23.6mmol) and 2M K₂CO₃ (35.5mmol, 71mmol) in dioxane (20ml) was added dichlorobis(triphenylphosphine)palladium (II) (415mg, 0.6mmol) under Ar. It was refluxed for 2hrs. After the removal of the solvent, the residue was neutralized by 1N HCl and extracted with dichloromethane. The organic layer was dried over MgSO₄ and concentrated *in vacuo* to give 4-[(2-methylthio)phenyl]benzoic acid (5.9g, 100%). ES-MS (M+H)⁺=245.

Step 2: To a solution of 4-[(2-methylthio)phenyl]benzoic acid (3.43g, 14mmol) in H₂O (10ml) and acetone (20ml) was added oxone monopersulfate (34.6g, 56mmol). The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was dried over MgSO₄ and concentrated *in vacuo* to give 2.16g (63%) 4-[(2-methylsulfonyl)phenyl]benzoic acid. ES-MS (M+H)⁺=277.

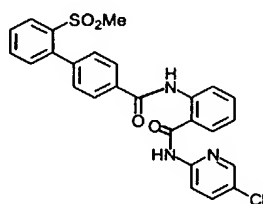
Step 3: To a solution of 4-[(2-methylsulfonyl)phenyl]benzoic acid (552mg, 2mmol) in dichloromethane (5ml) was added oxalyl chloride (350ul, 4mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent *in vacuo*, the residue was dissolved in dichloromethane (5ml), N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (700mg, 2.4mmol), pyridine (486ul, 6mmol) and catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 414mg (38%) of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-

methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. ES-MS $M^+=550$, $(M+2)^+=552$.

Example 30

5

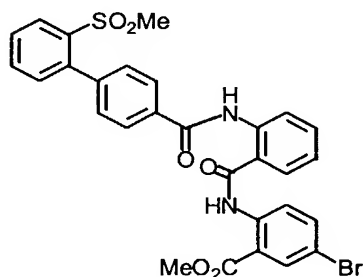
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



- 10 To a solution of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol) in dichloromethane (5ml) was added oxalyl chloride (175 ul, 2 mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent *in vacuo*, the residue was dissolved in dichloromethane (5ml), N-(5-chloro-2-pyridinyl)-(2-amino)phenylcarboxamide (297mg, 1.2 mmol), pyridine (243ul, 3 mmol) and
- 15 catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 95 mg (20%) of N-(5-chloro-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. ES-MS
- 20 $M^+=505.5$, $(M+2)^+=507.5$.

Example 31

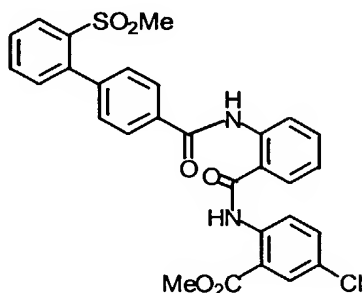
- N-(4-bromo-2-methoxycarbonylphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.**
- 25



A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was dissolved in 5 mL of dichloromethane, N-(4-bromo-2-methoxycarbonylphenyl)-(2-amino)phenylcarboxamide (348 mg, 1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column to give 480 mg (79%) of N-(4-bromo-2-methoxycarbonylphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. MS found for $C_{29}H_{24}BrN_2O_6S$ (M+H)⁺: 607.

Example 32

N-(4-chloro-2-methoxycarbonylphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.

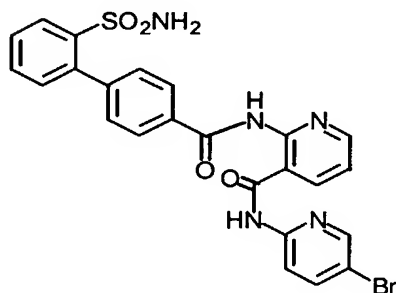


A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was dissolved in 5 mL of dichloromethane, N-(4-chloro-2-methoxycarbonylphenyl)-(2-amino)phenylcarboxamide (304 mg, 1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column to give 479 mg (85%) of N-(4-chloro-2-methoxycarbonylphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. MS found for $C_{29}H_{24}ClN_2O_6S$ (M+H)⁺: 563.

Example 33

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.

5



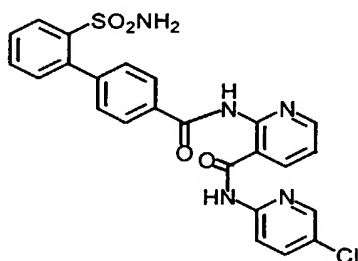
Step 1: A solution of 2-aminopyridine-3-carboxylic acid (138 mg, 1 mmol) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid and POCl₃. The resulting mixture was stirred at rt overnight, quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and flash chromatographed to give methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (243 mg, 52%). MS found for C₂₄H₂₆N₃O₅S (M+H)⁺: 468.

Step 2: To A solution of 2-amino-5-bromopyridine (45 mg, 4.0 equiv) in 5 mL of methylene chloride treated with AlMe₃ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (30 mg, 0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over MgSO₄, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (17 mg, 48%). MS found for C₂₄H₁₉BrN₅O₄S (M+H)⁺: 552.

Example 34

N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.

5

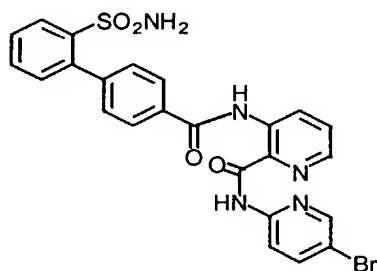


To A solution of 2-amino-5-chloropyridine (32 mg, 4.0 equiv) in 5 mL of methylene chloride treated with AlMe_3 (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (30 mg, 0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over MgSO_4 , filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (21 mg, 66%). MS found for $\text{C}_{24}\text{H}_{19}\text{ClN}_5\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 508.

20

Example 35

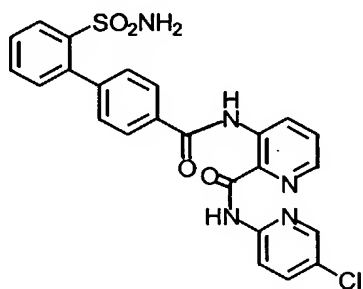
N-(5-bromo-2-pyridinyl)-(3-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide.



To A solution of 2-amino-5-bromopyridine (69.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with AlMe_3 (2M in hexane, 1 mL, 20 equiv) for 30 min was added 3-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-2-carboxylate (46.7 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over MgSO_4 , filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ gave N-(5-bromo-2-pyridinyl)-(3-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide (29 mg, 53%). MS found for $\text{C}_{24}\text{H}_{19}\text{BrN}_5\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 552.

Example 36

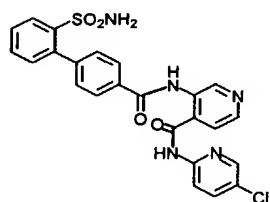
N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.



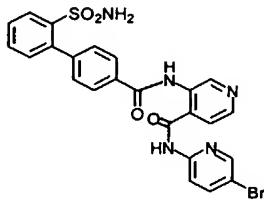
To A solution of 2-amino-5-chloropyridine (51.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with AlMe_3 (2M in hexane, 1 mL, 20 equiv) for 30 min was added 3-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-2-carboxylate (46.7 mg, 0.1mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over MgSO_4 , filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (33 mg, 64%). MS found for $\text{C}_{24}\text{H}_{19}\text{ClN}_5\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 508.

Examples 37-40

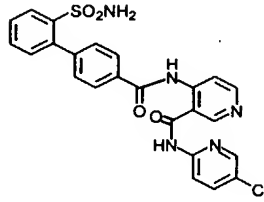
The following compounds of Examples 37-40 were prepared using the procedure described in Example 36:

Example 37

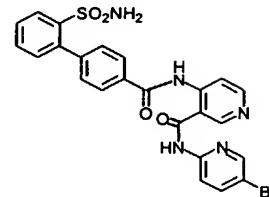
MS (M+H):
508

Example 38

MS (M+H):
552

Example 39

MS (M+H):
508

Example 40

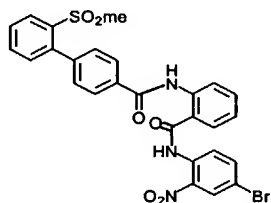
MS (M+H):
552

5

Example 41

N-(4-bromo-2-nitrophenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.

10



15

Step 1: A mixture of methyl 2-aminobenzoate (150 mg, 1 mmol, 1.0 equiv), 4-[(2-methylsulfonyl)phenyl]benzoic chloride (294 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered and evaporated. Flash chromatography on silica gel gave methyl 2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)aminobenzoate (250 mg, 54%). MS found for C₂₅H₂₇N₂O₅S (M+H)⁺: 467.

20

Step 2: To a solution of 4-bromo-2-nitroaniline (43.4 mg, 0.2 mmol, 2.0 equiv) in 5 mL of methylene chloride treated with AlMe₃ (2M in hexane, 0.3 mL, 6 equiv) for 30

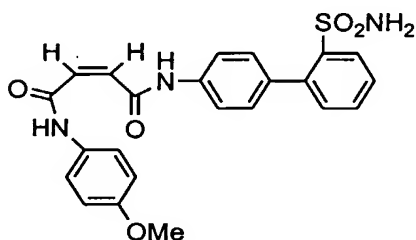
min was added methyl 2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)aminobenzoate (46.6 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over MgSO_4 , filtered and evaporated.

- 5 Flash chromatography on silica gel gave N-(4-bromo-2-nitrophenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide (5 mg, 9%). MS found for $\text{C}_{27}\text{H}_{21}\text{BrN}_3\text{O}_6\text{S}$ ($\text{M}+\text{H}$)⁺: 594.

Example 42

10

N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide



- 15 A. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide.

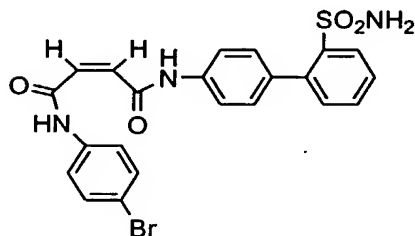
- To a solution of commercially available N-(4-methoxyphenyl)maleamic acid (100 mg, 0.452 mmol), triethylamine (0.126 mL, 0.906 mmol) and 4-(2-tert-butylaminosulfonylphenyl)aniline (138 mg, 0.454 mmol) in anhydrous DMF (5 mL),
- 20 BOP (260 mg, 0.588 mmol) was added. The mixture was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with H_2O , then with 5% NaHCO_3 , dried over Na_2SO_4 , concentrated in vacuo. The residue was purified by HPLC using a gradient of 20% CH_3CN in H_2O (containing 0.1% TFA) to 100% CH_3CN over 80 min. Fractions containing the desired product
- 25 were pooled, and lyophilized to give a powder (70 mg, yield: 31%). MS 508 ($\text{M} + \text{H}$).

B. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

The compound N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide (40 mg, 79 μ mol) was dissolved in TFA (3 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH₃CN in H₂O (containing 0.1% TFA) to 95% CH₃CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (18 mg, yield: 51%). MS 452 (M + H) and 474 (M + Na). ¹H NMR (CDCl₃) 11.40 (br.s, 1H), 10.28 (br.s, 1H), 8.12 (d, 1H, J = 8 Hz), 7.72 (d, 2H, J = 8 Hz), 7.60 – 7.20 (m, 9H), 6.86 (AB type, 2H), 6.45 (br.s, 2H), 3.79 (s, 3H).

Example 43

N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.



A. Preparation of N-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic methyl ester.

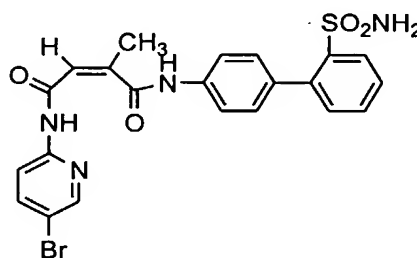
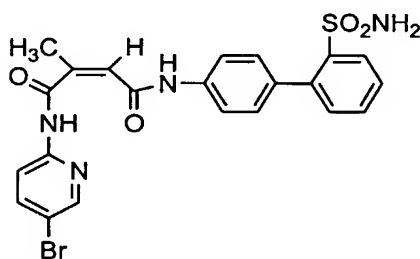
To a solution of commercially available maleic acid monomethyl ester (277 mg, 2.13 mmol), 4-(2-tert-butylaminosulfonyl)aniline (648 mg, 2.13 mmol) and triethylamine (0.593 mL, 4.26 mmol) in CH₂Cl₂ (20 mL), BOP (1.13 g, 2.55 mmol) was added. The mixture was stirred at room temperature overnight. More maleic acid monomethyl ester (50 mg, 0.385 mmol) was added. It was stirred for 3 hours. The CH₂Cl₂ solution was then washed with sat. NaHCO₃, 1N HCl and sat. NaCl. The solution was dried over Na₂SO₄, concentrated in vacuo. The residue was purified by a silica gel column using a gradient of 10-40% EtOAc in hexane as solvents, to give the titled compound (360 mg, yield: 41%). MS 361 (M + H - ^tBu) and 439 (M + Na).

B. Preparation of N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

To a solution of 4-bromoaniline (93 mg, 0.543 mmol) in CH₂Cl₂ (5 mL) at room temperature, trimethylaluminum (0.82 mL, 2.0 M in hexane, 1.64 mmol) was added dropwise. After the solution was stirred for 30 min at room temperature, compound N-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)maleamic methyl ester (113 mg, 0.272 mmol) was added. The mixture was stirred at room temperature for 2 days. The solution was neutralized with 1N HCl to pH 2-3. Water and CH₂Cl₂ were added, and organic phase was separated, dried over Na₂SO₄, concentrated in vacuo. The residue was dissolved in TFA (4 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH₃CN in H₂O (containing 0.1% TFA) to 95% CH₃CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (8 mg, yield: 6%). MS 500 and 502 (M + H), 522 and 524 (M + Na). ¹H NMR (CD₃OD) 8.09 (d, 1H, J = 8 Hz), 7.68 (d, 2H, J = 8 Hz), 7.64 – 7.28 (m, 9H), 6.45 (AB type, 2H).

Examples 44 and 45

Preparation of N¹-(5-bromopyridin-2-yl)-N⁴-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and N¹-(5-bromopyridin-2-yl)-N⁴-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.



A. Preparation of N-(5-bromopyridin-2-yl)-methylmaleimide.

A mixture of citraconic anhydride (1.00 mL, 11.1 mmol) and 2-amino-5-bromopyridine (1.93 g, 11.2 mmol) in toluene (60 mL) was heated to reflux overnight.

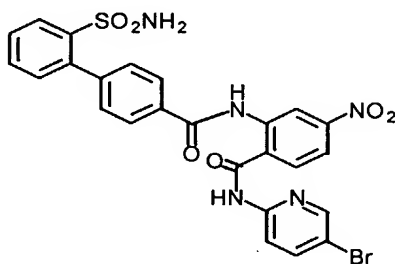
The solution was cooled down, filtered. The filtrate was concentrated in vacuo to give a solid (2.10 g, yield: 71%). MS 267 and 269 (M + H).

- B. Preparation of N¹-(5-bromopyridin-2-yl)-N⁴-(4-[(2-aminosulfonyl)phenyl] phenyl)-2-methylmaleamic amide and N¹-(5-bromopyridin-2-yl)-N⁴-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.

- To the solution of 4-(2-aminosulfonylphenyl)aniline (0.170 g, 0.685 mmol) in CH₂Cl₂ (10 mL) at room temperature, trimethylaluminum (2.0 M in hexane, 2.00 mL, 4.00 mmol) was added dropwise, during which time, white gel-like precipitates came out the solution. It was stirred for 30 min. A solution of N-(5-bromopyridin-2-yl)-methylmaleimide (0.122 g, 0.457 mmol) in CH₂Cl₂ (5 mL) was added. It was stirred for 1 hour, during which time the precipitates started to dissolve, and the solution became clear. It was stirred for another 2 hours. 1N HCl was added to neutralize the solution to pH 2-3, which resulted in precipitation. The precipitates were collected by filtration, dried on vacuum. The precipitates (75 mg, yield: 32%) were a mixture of 2-methyl and 3-methylmaleamic amide isomers in a ratio of 1 : 5. MS 515 and 517 (M + H), 537 and 539 (M + Na).

20 Example 46

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenyl)phenylcarbonyl)amino)-4-nitrophenylcarboxamide.



25

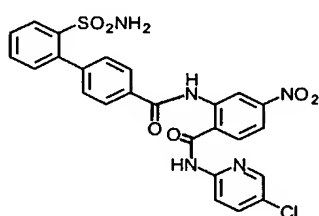
Step 1: A solution of 2-amino-4-nitrobenzoic acid (182 mg, 1 mmol, 1 equiv) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1

equiv) and POCl_3 (0.93 mL, 10 equiv). The resulting mixture was stirred at rt overnight, quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over MgSO_4 , filtered and flash chromatographed to give methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)amino-4-nitrobenzoate (430 mg, 84%). MS found for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_7\text{S}$ ($\text{M}+\text{H}$)⁺: 512.

Step 2: To A solution of 2-amino-5-bromopyridine (135 mg, 4.0 equiv) in 5 mL of methylene chloride treated with AlMe_3 (2M in hexane, 1 mL, 10 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)amino-4-nitrobenzoate (100 mg, 0.2 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over MgSO_4 , filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ gave N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide (42 mg, 36%). MS found for $\text{C}_{25}\text{H}_{19}\text{BrN}_5\text{O}_6\text{S}$ ($\text{M}+\text{H}$)⁺: 596.

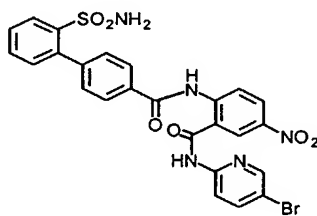
Examples 47-49

The following compounds of Examples 47-49 were prepared according to the procedure described in example 46.



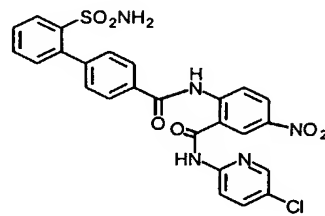
Example 47

MS ($\text{M}+\text{H}$):
552



Example 48

MS ($\text{M}+\text{H}$):
596



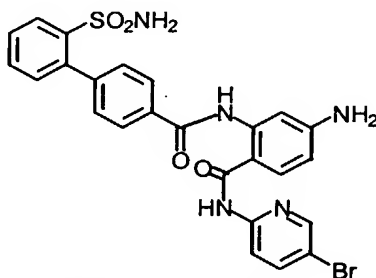
Example 49

MS ($\text{M}+\text{H}$):
552

Example 50

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide.

5

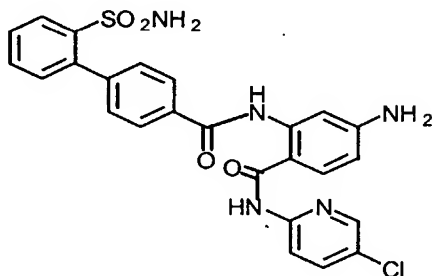


A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-nitrophenylcarboxamide (65 mg, 0.1 mmol, 1 equiv) in 10 mL of EtOAc was treated with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (90 mg, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous NaHCO_3 and 1N NaOH. The organic layer was dried over MgSO_4 , filtered and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-aminophenyl carboxamide, which was refluxed with 2 mL of TFA for 1h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide (47 mg, 84%). MS found for $\text{C}_{25}\text{H}_{21}\text{BrN}_5\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 566.

20

Example 51

N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide.

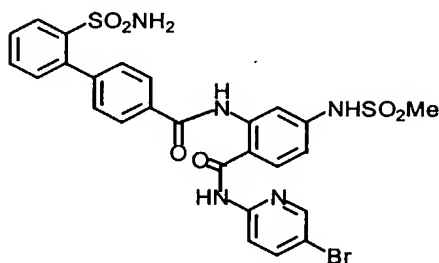


This compound was prepared according to the procedure described in example 50. MS found for $C_{25}H_{21}ClN_5O_4S$ (M+H)⁺: 522.

Example 52

5

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide.



10

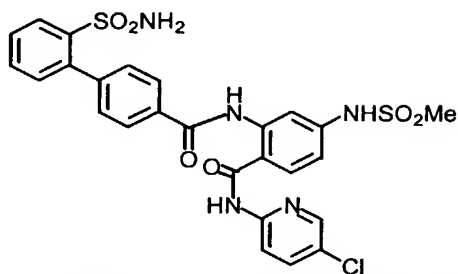
A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-aminophenyl carboxamide (62 mg, 0.1mmol, 1 equiv) in 3 mL of CH_2Cl_2 was treated with $MsCl$ (23 mg, 2 equiv) and TEA (0.5 mL) at rt for 4 h. The mixture was washed with water and dried over

15 $MgSO_4$, filtered and evaporated. The residue was refluxed with 2 mL of TFA for 1h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide (33 mg, 52%). MS found for

20 $C_{26}H_{23}BrN_5O_6S_2$ (M+H)⁺: 644.

Example 53

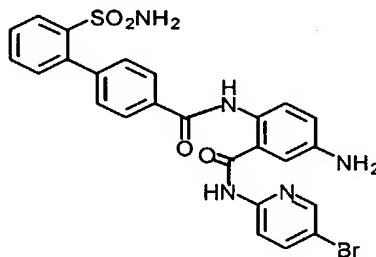
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide.



This compound was prepared according to the procedure described in example 53. MS found for $C_{26}H_{23}ClN_5O_6S_2$ (M+H)⁺: 600.

10 Example 54

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide.



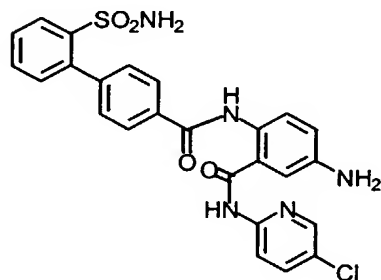
15

This compound was prepared according to the procedure described in example 50. MS found for $C_{25}H_{21}BrN_5O_4S$ (M+H)⁺: 566.

Example 55

N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide.

5



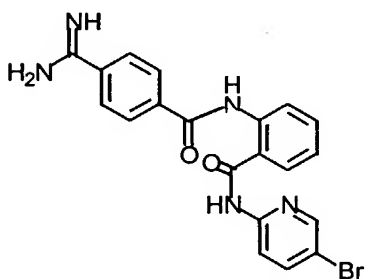
This compound was prepared according to the procedure described in example 50. MS found for $C_{25}H_{21}ClN_5O_4S$ ($M+H$)⁺: 522.

10

Example 56

N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide.

15



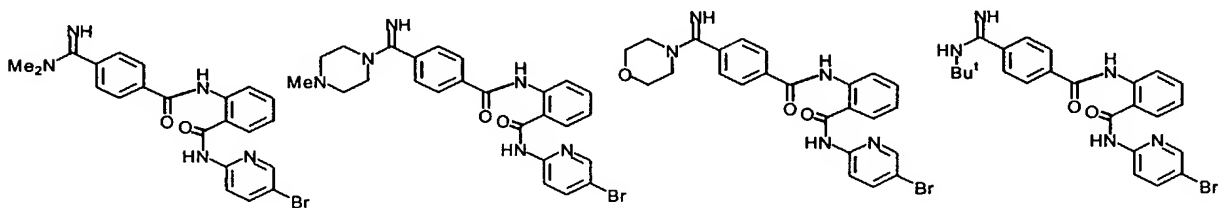
Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-cyano benzoyl chloride (165 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H₂O. The organic layer was dried over MgSO₄, filtered, evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (349 mg, 70%). MS found for $C_{20}H_{14}BrN_4O_2$ ($M+H$)⁺: 421.

20

Step 2: A stream of HCl(g) was bubbled through a 0°C solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and
 5 evaporated. The resulting residue was treated with ammonium acetate (40 mg) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide (31 mg, 70%). MS found for
 10 C₂₀H₁₇BrN₅O₂ (M+H)⁺: 438.

Examples 57-86

The following compounds of Examples 57-86 were prepared according to the
 15 procedure described in example 56.



Example 57

MS (M+H):
466

Example 58

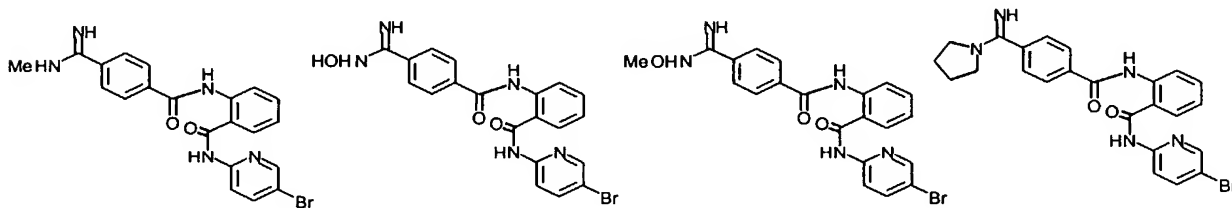
MS (M+H):
521

Example 59

MS (M+H):
508

Example 60

MS (M+H):
494



Example 61

MS (M+H):
452

Example 62

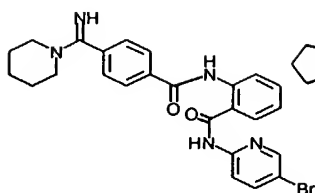
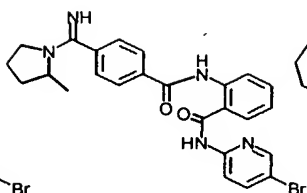
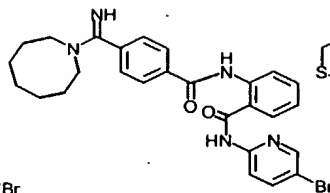
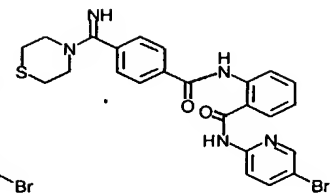
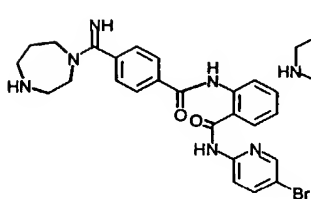
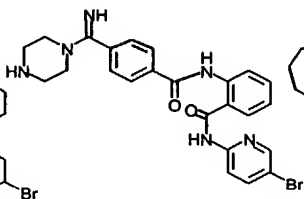
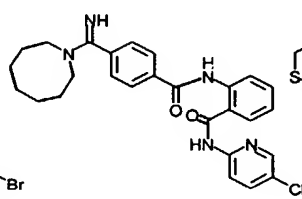
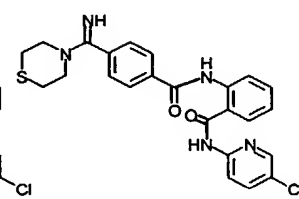
MS (M+H):
454

Example 63

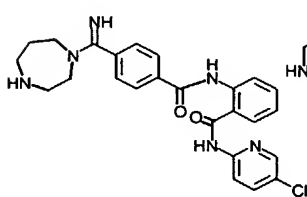
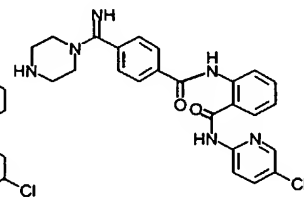
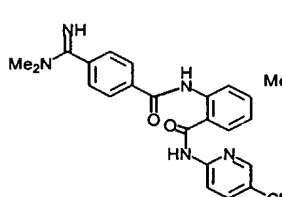
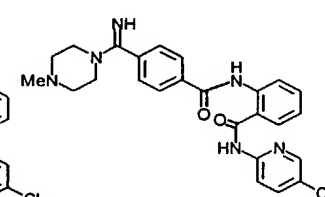
MS (M+H):
468

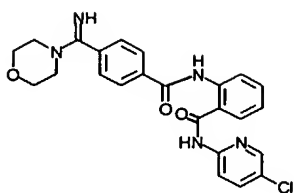
Example 64

MS (M+H):
492

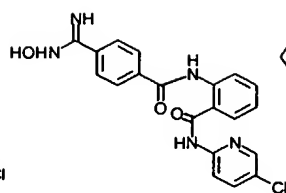
Example 65MS (M+H):
506Example 66MS (M+H):
506Example 67MS (M+H):
520Example 68MS (M+H):
524Example 69MS (M+H):
521Example 70MS (M+H):
507Example 71MS (M+H):
476Example 72MS (M+H):
480

5

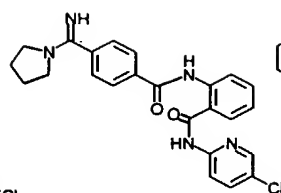
Example 73MS (M+H):
477Example 74MS (M+H):
463Example 75MS (M+H):
422Example 76MS (M+H):
477

Example 77

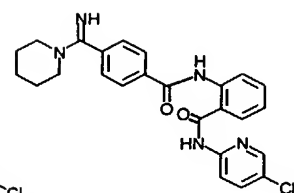
MS (M+H):
464

Example 78

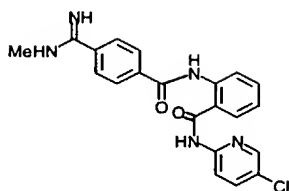
MS (M+H):
410

Example 79

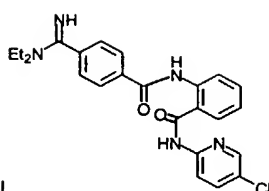
MS (M+H):
448

Example 80

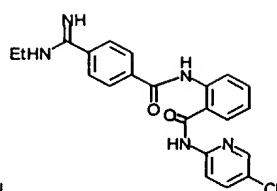
MS (M+H):
462

Example 81

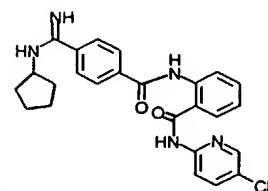
MS (M+H): 408

Example 82

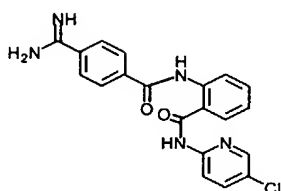
MS (M+H): 22

Example 83

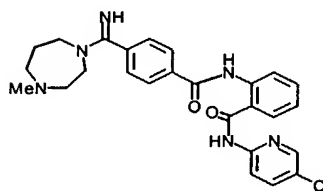
MS (M+H): 450

Example 84

MS (M+H): 462

Example 85

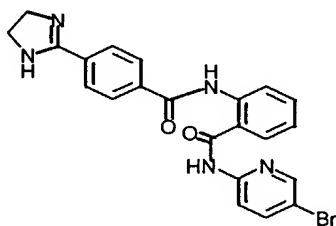
MS (M+H): 394

Example 86

MS (M+H): 491

5 Example 87

N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazolinyl)phenylcarbonyl)amino)-phenylcarboxamide.



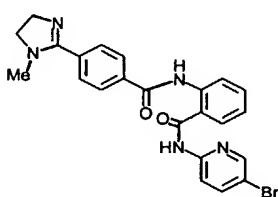
10

A stream of HCl(g) was bubbled through a 0°C solution of N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazolinyl)phenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The

- resulting residue was treated with ethylene diamine (40 mg) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazolinyl)phenylcarbonyl)amino)-phenylcarboxamide (41 mg, 89%). MS found for C₂₂H₁₉BrN₅O₂ (M+H)⁺: 464.
- 5

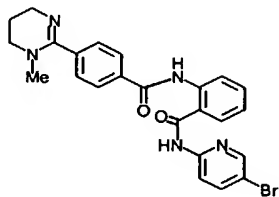
Examples 88-96

- 10 The following compounds of Examples 88-96 were prepared according to the procedure described in example 87.



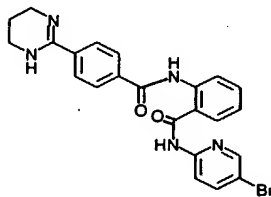
Example 88

MS (M+H): 478



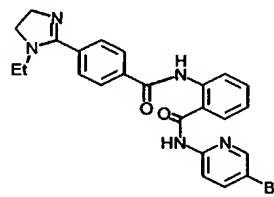
Example 89

MS (M+H): 492



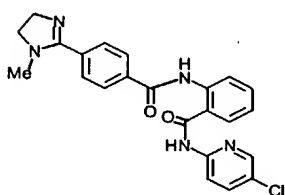
Example 90

MS (M+H): 478



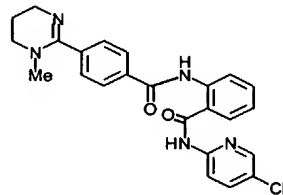
Example 91

MS (M+H): 492



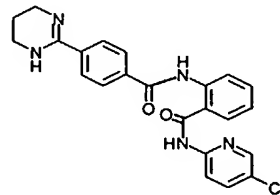
Example 92

MS (M+H): 434



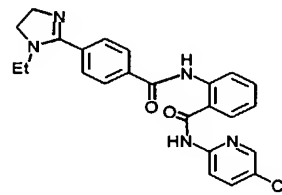
Example 93

MS (M+H): 448



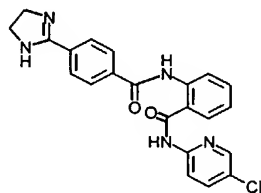
Example 94

MS (M+H): 434



Example 95

MS (M+H): 448

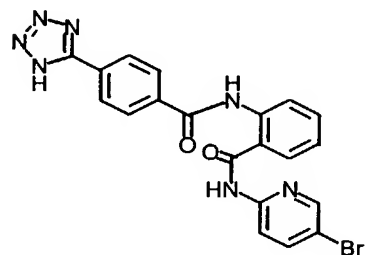


Example 96

MS (M+H): 420

Example 97

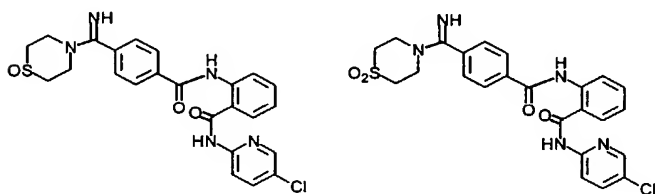
N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide.



A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) and sodium azide (67 mg, 10 equiv) in 5 mL of DMF was heated at 100°C for 24h. The reaction mixture was diluted with EtOAc, washed with water, dried, filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide (33 mg, 65%). MS found for C₂₀H₁₅BrN₇O₂ (M+H)⁺: 464.

Example 98 and Example 99

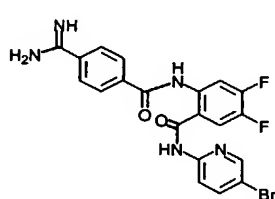
N-(5-bromo-2-pyridinyl)-(2-(4-[1,1-doxo(1,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl)amino)-phenylcarboxamide and N-(5-bromo-2-pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl)amino)-phenylcarboxamide.



A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-(1,4-thiazaperhydroin-4-yl)iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (48 mg, 0.1 mmol) and 3 mL of 30% hydrogen doxide was stirred at rt for 12h. The reaction was quenched with solid $\text{Na}_2\text{S}_2\text{O}_3$. Purification by HPLC (C18 reversed phase) eluting with 0.5% TFA in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ gave N-(5-bromo-2-pyridinyl)-(2-(4-[1,1-doxo(1,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (15 mg, 31%), MS found for $\text{C}_{24}\text{H}_{23}\text{ClN}_5\text{O}_4\text{S}$ ($\text{M}+\text{H}$)⁺: 512 and N-(5-bromo-2-pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (20 mg, 41%). MS found for $\text{C}_{24}\text{H}_{23}\text{ClN}_5\text{O}_3\text{S}$ ($\text{M}+\text{H}$)⁺: 496.

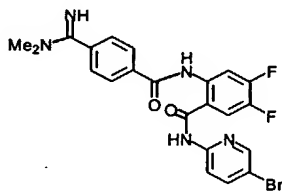
Examples 100-105

The following compounds were prepared according to the procedure described in example 56 and example 87.



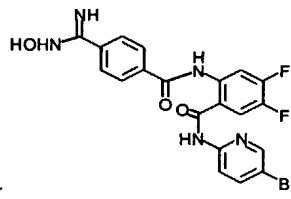
Example 100

MS ($\text{M}+\text{H}$): 474



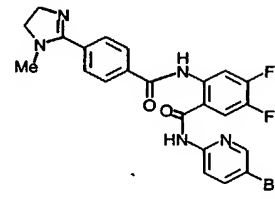
Example 101

MS ($\text{M}+\text{H}$): 502



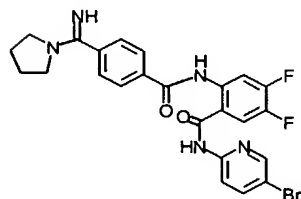
Example 102

MS ($\text{M}+\text{H}$): 490



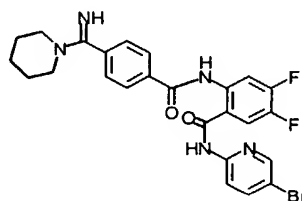
Example 103

MS ($\text{M}+\text{H}$): 514



Example 104

MS ($\text{M}+\text{H}$): 528

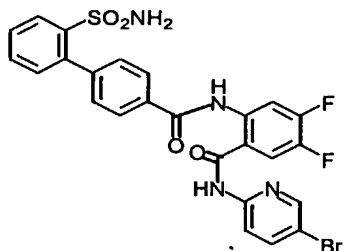


Example 105

MS ($\text{M}+\text{H}$): 542

Example 106

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)-
4,5-difluorophenylcarboxamide.



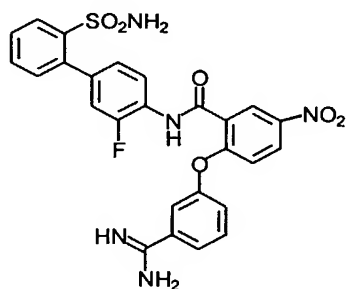
This compound is prepared according to the procedure described in example 27. MS
 found for $C_{25}H_{18}BrF_2N_4O_4S$ ($M+H$)⁺: 587.

10

Example 107

3-(2-(4-[(2-aminosulfonyl)phenyl]-2-fluorophenylaminocarbonyl)-4-
aminophenoxy) benzamidine.

15

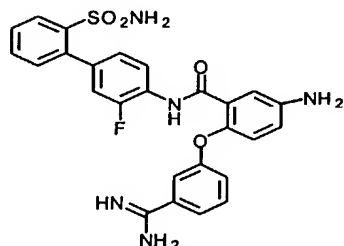


This compound is prepared according to the procedure described in example 17. MS
 found for $C_{26}H_{21}FN_5O_6S$ ($M+H$)⁺: 550.

20

Example 108

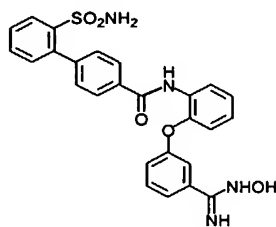
3-(2-(4-[(2-aminosulfonyl)phenyl]-2-fluorophenylaminocarbonyl-4-aminophenoxy) benzamidine).



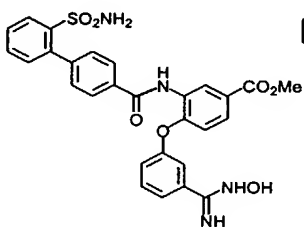
- 5 This compound is prepared according to the procedure described in example 18. MS found for $C_{26}H_{23}FN_5O_4S$ (M+H)⁺: 520.

Examples 109-114

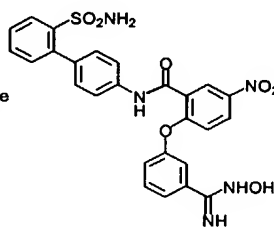
- 10 The following compounds were prepared according to the procedure described in example 1 except that in step 4, NH_2OH was used instead of NH_4OAc .

Example 109

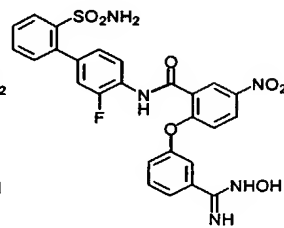
MS (M+H): 502

Example 110

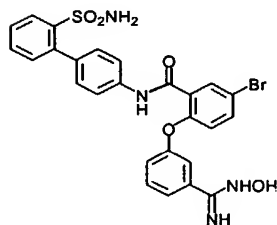
MS (M+H): 560

Example 111

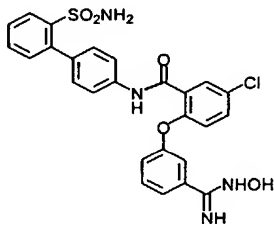
MS (M+H): 547

Example 112

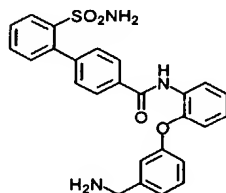
MS (M+H): 547

Example 113

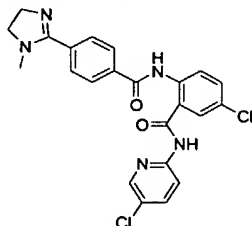
MS (M+H): 581

Example 114

MS (M+H): 537

Example 115**3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzylamine.**

- 5 A mixture of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy)benzonitrile (53 mg, 0.1 mmol) (53 mg, 0.1 mmol, 1 equiv), 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H₂ atmosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, residue was refluxed in 2 mL of TFA for 1h, and purified
- 10 by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzylamine (13 mg, 27%). MS found for C₂₆H₂₄N₃O₄S (M+H)⁺: 474.

Example 116

15

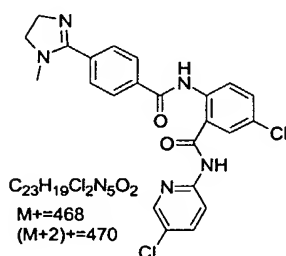
- Step 1: To a solution of 2-amino-5-chloropyridine (328mg, 2.55mmol) in tetrahydrofuran (5ml) was 0.5M potassium bis(trimethylsilyl)amide in toluene (10ml, 5.05mmol) dropwise at -78 °C. After stirred for additional 0.5hr at -78 °C, the mixture was added 5-chloroisatoic anhydride (0.5g, 2.55mmol) at -78 °C. The mixture was
- 20 warmed up to r.t gradually and stirred overnight. After quenched by saturated ammonium chloride solution, the mixture was extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71g, 100%). MS found for C₁₂H₉Cl₂N₃O M⁺=282, (M+2)⁺=284.

Step 2: To a solution of the compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71g, 2.52mmol) in dichloromethane (10ml) was added 3-cyanobenzoyl chloride (417mg, 2.52mmol) and pyridine (0.611ml, 7.55mmol). The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with dichloromethane to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide as a solid (683mg, 66%). MS found for C₂₀H₁₂Cl₂N₄O₂ M⁺=411, (M+2)⁺=413.

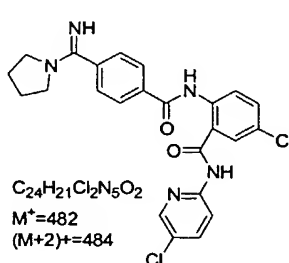
Step 3: To a solution of the compound of N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (683mg, 1.66mmol) in anhydrous pyridine (10ml) and triethyl amine (1ml) was saturated with hydrogen sulfide gas at 0 °C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous acetone (5ml) and iodomethane (1ml, 16.6mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the residue was dissolved in anhydrous methanol (5ml) and added a solution of N-methylethylenediamine (0.732ml, 8.3mmol) and acetic acid (1.5ml) in anhydrous methanol (5ml). The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder. MS found for C₂₃H₁₉Cl₂N₅O₂ M⁺=468 (M+2)⁺=470.

Examples 117-141

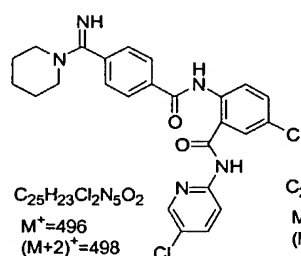
The following compounds were prepared according to the procedure described in example 116.



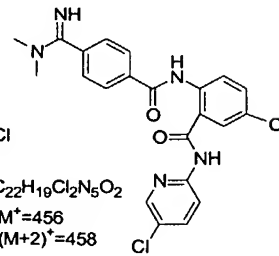
Example 117



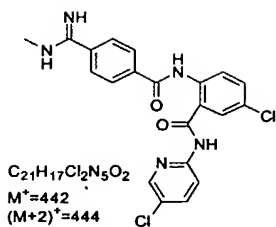
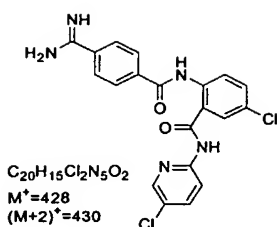
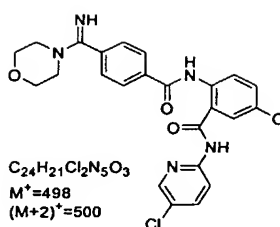
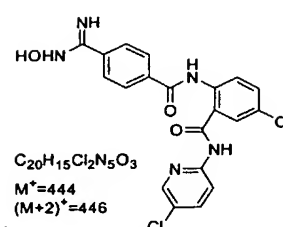
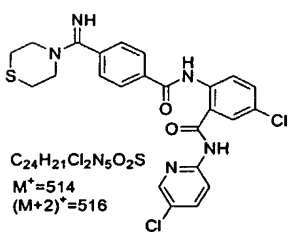
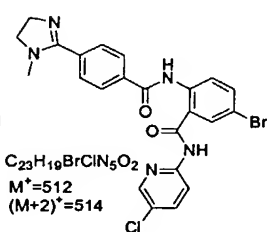
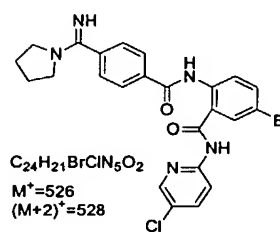
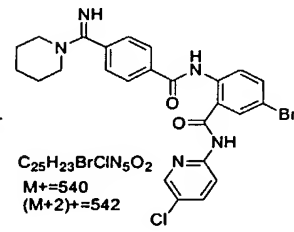
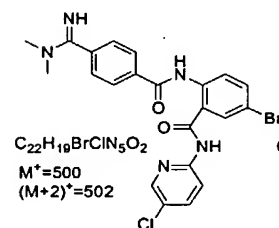
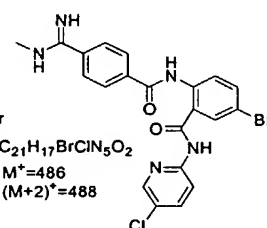
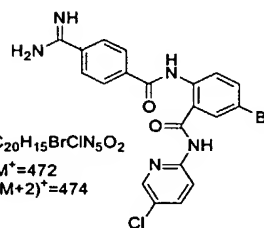
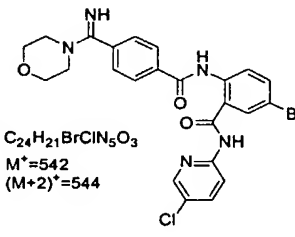
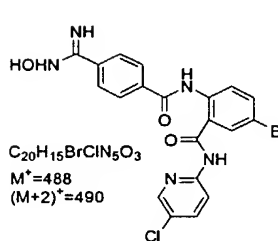
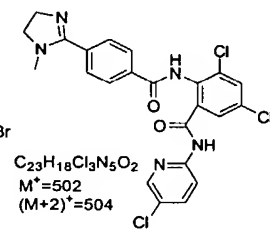
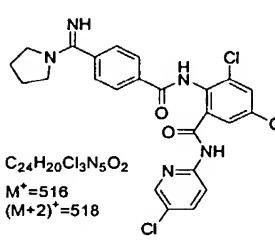
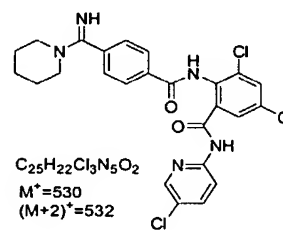
Example 118

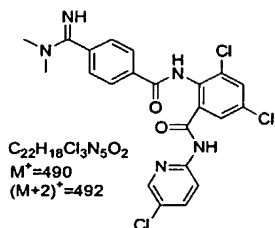
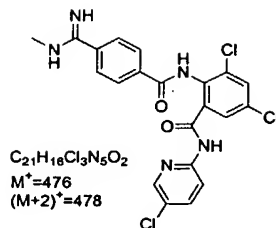
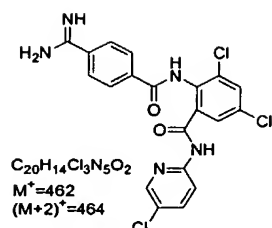
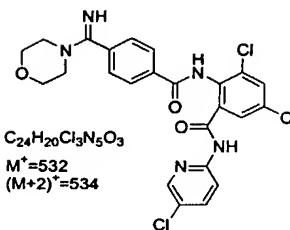
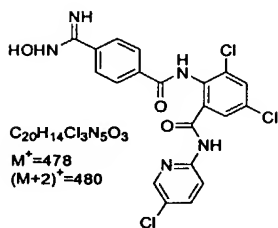


Example 119

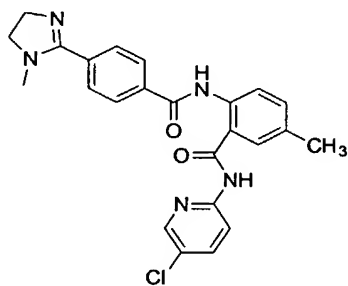


Example 120

Example 121Example 122Example 123Example 124Example 125Example 126Example 127Example 128Example 129Example 130Example 131Example 132Example 133Example 134Example 135Example 136

Example 137Example 138Example 139Example 140Example 141

5

Example 142

Step 1: To a solution of 5-methyl-2-nitrobenzoic acid (1g, 5.52mmol) in dichloromethane (5ml) was added oxalyl chloride (0.964ml, 11.04mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5ml). 2-amino-5-chloropyridine (852mg, 6.62mmol) and pyridine (1.34ml, 16.56mmol) were

10

added to the solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide as a solid (1.48g, 92%). MS found for
5 C₁₃H₁₀ClN₃O₃ M⁺=291, (M+2)⁺=293.

Step 2: To a solution of the compound of N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide (1.48g, 5.1mmol) in methanol (10ml) was added 5% Pt/C
10 (1.48g, 0.19mmol). The mixture was applied hydrogen balloon at r.t. for 2 hrs. After the filtration by Celite, the filtrate was concentrated to give (2-aminophenyl)-N-(2-pyridyl)carboxamide, C, chloride, N (1.36g, 100%). MS found for C₁₃H₁₂ClN₃O M⁺=262, (M+2)⁺=264.

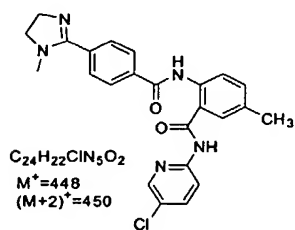
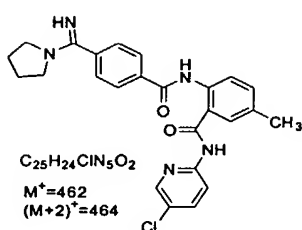
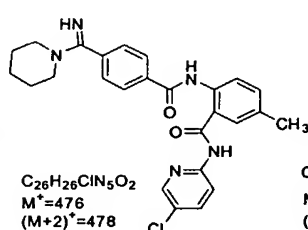
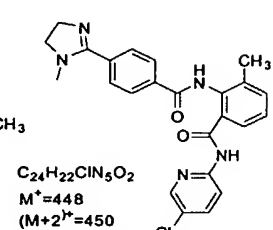
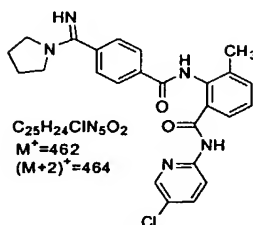
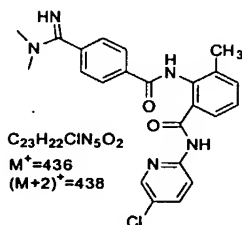
15 Step 3: To a solution of the compound of (2-aminophenyl)-N-(2-pyridyl)carboxamide, C, chloride, N (1.36g, 5.2mmol) in dichloromethane (10ml) was added 3-cyanobenzoyl chloride (860mg, 5.2mmol) and pyridine (1.26ml, 15.6mmol). The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude
20 residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}(4-cyanophenyl)carboxamide as a solid (830mg, 41%). MS found for C₂₁H₁₅ClN₄O₂ M⁺=390, (M+2)⁺=392.

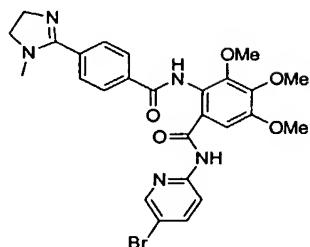
25 Step 4: To a solution of the compound of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}(4-cyanophenyl)carboxamide (830mg, 2.1mmol) in anhydrous methanol (5ml) and ethyl acetate (10ml) was saturated with hydrogen chloride gas at 0 °C. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the
30 residue was dissolved in anhydrous methanol (5ml) and N-methylethylenediamine (0.926ml, 10.5mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder. MS found for
35 C₂₄H₂₂ClN₅O₂ M⁺=448, (M+2)⁺=450.

Examples 143-148

The following compounds were prepared according to the procedure described in Example 142.

5

Example 143Example 144Example 145Example 146Example 147Example 148

Example 149

Step 1: To a solution of 3,4,5-trimethoxy-2-nitrobenzoic acid (0.5g, 1.95mmol) in
5 dichloromethane (5ml) was added oxalyl chloride (0.34ml, 3.9mmol) and a few drops
of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation
of the solvent, the residue was dissolved in dichloromethane (5ml). 2-amino-5-
bromopyridine (0.81g, 4.7mmol) and pyridine (0.94ml, 11.7mmol) were added to the
solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent,
10 the crude residue was purified by silica gel column chromatography using solvent
system 25% ethyl acetate in hexane as eluent to give N-(5-bromo(2-pyridyl))(3,4,5-
trimethoxy-2-nitrophenyl)carboxamide as a solid (790mg, 98%). MS found for
C₁₅H₁₄BrN₃O₆ M⁺=412, (M+2)⁺=414.

15
Step 2: To a solution of the compound of N-(5-bromo(2-pyridyl))(3,4,5-trimethoxy-2-
nitrophenyl)carboxamide (790mg, 1.92mmol) in ethyl acetate (5ml) was added tin
chloride (II) hydrate (1.73g, 7.67mmol). The mixture was stirred under reflux
condition for 2 hrs. After filtered by Celite, the filtrate was added 1N sodium
20 hydroxide solution and extracted with ethyl acetate. The organic layer was dried over
magnesium sulfate and concentrated to give (2-amino-3,4,5-trimethoxyphenyl)-N-(5-
bromo(2-pyridyl))carboxamide (570mg, 77%). MS found for C₁₅H₁₆BrN₃O₄
M⁺=382, (M+2)⁺=384.

25
Step 3: To a solution of the compound of (2-amino-3,4,5-trimethoxyphenyl)-N-(5-
bromo(2-pyridyl))carboxamide (570mg, 1.49mmol) in dichloromethane (5ml) was
added 3-cyanobenzoyl chloride (247mg, 1.49mmol) and pyridine (0.362ml,
4.48mmol). The mixture was stirred at r.t. overnight. After the evaporation of the
30 solvent, the crude residue was purified by silica gel column chromatography using

solvent system 25% ethyl acetate in hexane as eluent to give N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}(4-cyanophenyl)carboxamide as a solid (680mg, 69%). MS found for C₂₃H₁₉BrN₄O₅ M⁺=511, (M+2)⁺=513.

5

Step 4: To a solution of the compound of N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}(4-cyanophenyl)carboxamide (680mg, 1.33mmol) in anhydrous methanol (5ml) and ethyl acetate (10ml) was saturated with hydrogen chloride gas at 0 °C. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the residue was dissolved in anhydrous methanol (5ml) and N-methylethylenediamine (0.586ml, 6.65mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder (240mg, 32%). MS found for C₂₆H₂₆BrN₅O₅ M⁺=568, (M+2)⁺=570.

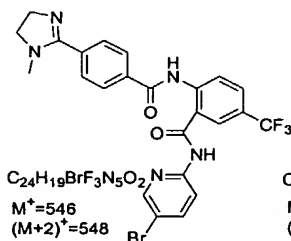
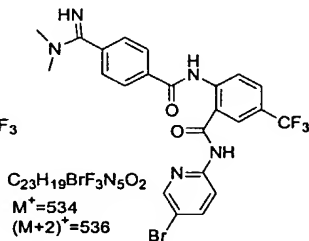
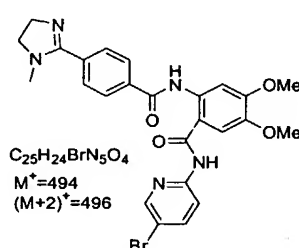
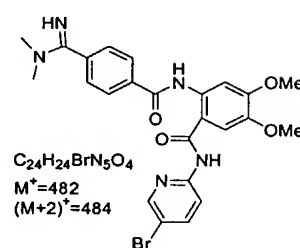
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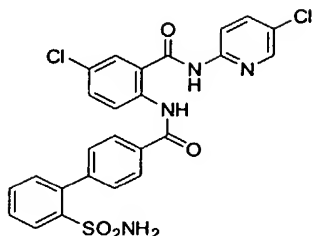
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Examples 150-153

The following compounds were prepared according to the procedure described in Example 149.

20

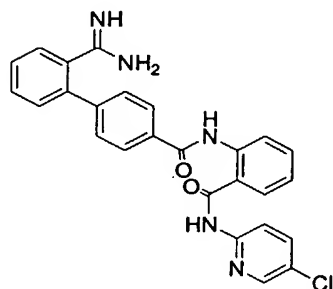
Example 150Example 151Example 152Example 153

Example 154

- Step 1: To a solution of 4-{2-[[*tert*-butylamino]sulfonyl]phenyl} benzoic acid
 5 (167mg, 0.5mmol) in dichloromethane (5ml) was added oxalyl chloride (0.09ml, 1mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5ml). The compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.17g, 0.6mmol) and pyridine (0.122ml, 1.5mmol) were added
 10 to the solution. The mixture was stirred at r.t. overnight. The solvent was evaporated to give (2-{[4-(2-[[*tert*-butylamino]sulfonyl]phenyl)phenyl]-carbonylamino}-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide. MS found for C₂₉H₂₆Cl₂N₄O₄S M⁺=597, (M+2)⁺=599.
- 15 Step 2: The mixture of the compound of (2-{[4-(2-[[*tert*-butylamino]sulfonyl]phenyl)phenyl] carbonylamino}-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide example 12 (0.5mmol) in trifluoroacetic acid (5ml) was stirred at r.t. for 5hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give
 20 N-(5-chloro(2-pyridyl))(5-chloro-2-{[4-(2-sulfamoylphenyl)phenyl]carbonylamino}phenyl)-carboxamide as a white powder (68mg, 25%). MS found for C₂₅H₁₈Cl₂N₄O₄S
 25 M⁺=541, (M+2)⁺=543.

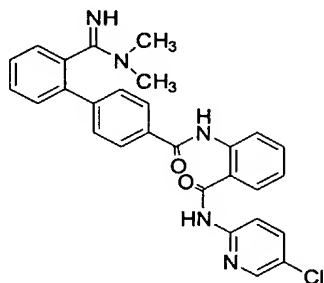
Example 155**2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]-benzenecarboxamidine**

5



$C_{26}H_{20}ClN_5O_2$
Exact Mass: 469.13
Mol. Wt.: 469.92

A stream of H_2S (g) was bubbled through a 0 °C solution of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl} [4-(2-cyanophenyl)phenyl]carboxamide (100 mg, 0.22 mmol, 1.0 equiv.) in 9 mL pyridine and 1 mL NEt_3 until saturation. The mixture was stirred at rt for 1 day and evaporated. The resulting residue was treated with MeI (94 mg, 0.663 mmol, 3.0 equiv.) in 10 mL acetone at reflux temperature for 1 hr and concentrated to dryness. The resulting residue was treated with a mixture of NH_4OAc (340 mg, 4.42 mmol, 20 equiv.) in 0.5 mL acetic acid and 2 mL methanol at 50 °C for 2 days. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN to give 2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]benzenecarboxamidine (15 mg, 15%). MS found for $C_{26}H_{20}ClN_5O_2$ ($M+H$)⁺: 470.

20 Example 156**(4-{2-[(dimethylamino)iminomethyl]phenyl}phenyl)-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide**

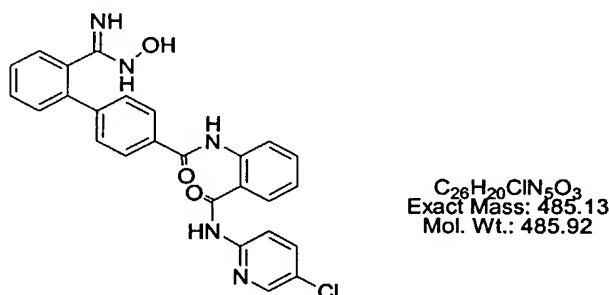
$C_{28}H_{24}ClN_5O_2$
Exact Mass: 497.16
Mol. Wt.: 497.98

This compound was prepared according to the procedure described in Example 155.
MS found for $C_{28}H_{24}ClN_5O_2$ ($M+H$)⁺: 498.

5 Example 157

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[2-((hydroxyamino)iminomethyl)-phenyl]phenyl}carboxamide

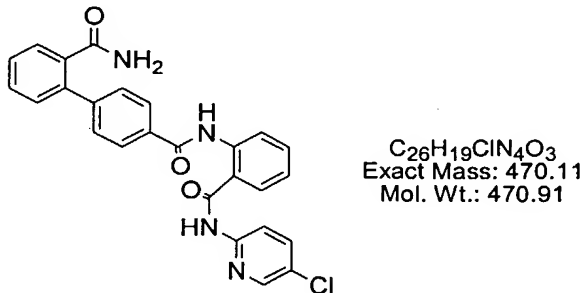
10



A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-(2-cyanophenyl)phenyl} carboxamide (14 mg, 0.03 mmol, 1.0 equiv.), hydroxyamine hydrochloride (6.25 mg, 0.09 mmol, 3.0 equiv.) and triethyl amine (0.03 mL, 0.3 mmol, 10.0 equiv.) in ethanol (3 mL) was stirred at rt for 6 days, concentrated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[2-((hydroxyamino)iminomethyl) phenyl] phenyl}carboxamide (4 mg, 27.5%).
MS found for $C_{26}H_{20}ClN_5O_3$ ($M+H$)⁺: 486.

20 Example 158

2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]benzamide

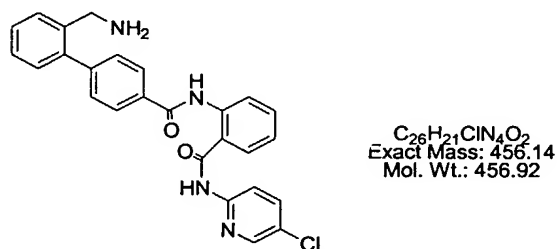


This compound was obtained as on of the side product in Example 157.

MS found for $C_{26}H_{19}ClN_4O_3$ (M+H)⁺: 471

5 Example 159

{4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-phenyl}carboxamide



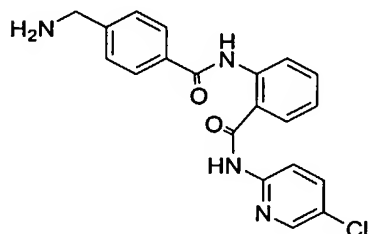
10

A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(2-cyanophenyl)phenyl] carboxamide (200 mg, 0.442 mmol, 1.0 equiv.), cobalt chloride (86 mg, 0.664 mmol, 1.5 equiv.) and sodium borohydride (50 mg, 1.33 mmol, 3.0 equiv.) in DMF (15 mL) was stirred at 0 °C to rt for 3 days. The reaction was

15 quenched with ice cubes, diluted with DCM (100 mL) and filtered through celite. The filtrate was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, evaporated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN gave {4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (87 mg, 43%). MS found for $C_{26}H_{21}ClN_4O_2$
20 (M+H)⁺: 457.

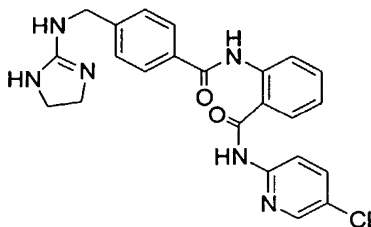
Example 160**[4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide**

5



$C_{20}H_{17}ClN_4O_2$
Exact Mass: 380.10
Mol. Wt.: 380.83

A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (1 g, 2.6 mmol, 1.0 equiv.), cobalt chloride (0.5 g, 3.85 mmol, 1.5 equiv.) and sodium borohydride (0.295 g, 7.8 mmol, 3.0 equiv.) in DMF (20 mL) was stirred at 0 °C to rt for 2.5 hr. The reaction was quenched with ice cubes, diluted with ethyl acetate (100 mL) and filtered through celite. The filtrate was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, evaporated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN gave [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (320 mg, 30%). MS found for $C_{20}H_{17}ClN_4O_2$ (M+H)⁺: 381.

Example 161**N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[(2-imidazolin-2-ylamino)methyl]-phenyl}carboxamide**

$C_{23}H_{21}ClN_6O_2$
Exact Mass: 448.14
Mol. Wt.: 448.90

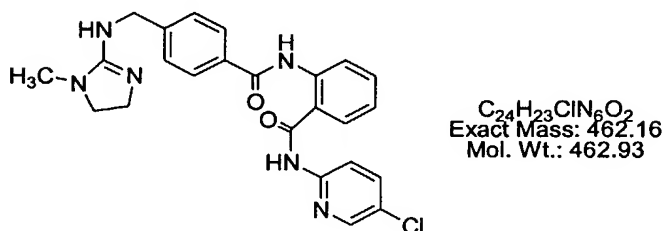
A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (80 mg, 0.21 mmol), 2-methylthio-2-imidazoline hydriodide (77 mg, 0.315 mmol, 1.5 equiv.) and triethyl amine (0.5 mL) in 1 mL DMF was stirred at room temperature overnight, concentrated to dryness and
 5 HPLC (C18 reversed phase) eluting with 0.1% TFA in H₂O/CH₃CN gave N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl} {4-[(2-imidazolin-2-ylamino)methyl]phenyl}carboxamide (13.5 mg, 15%). MS found for C₂₃H₂₁ClN₆O₂ (M+H)⁺: 449

10

Example 162

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-{[(1-methyl(2-imidazolin-2-yl))amino]methyl}phenyl)carboxamide

15



Step 1: To the boiling solution of 2-methylthio-2-imidazoline hydriodide (1 g, 8.4 mmol) in methanol (10 mL) was added MeI (0.78 mL, 12.6 mmol, 1.5 equiv.) dropwise. The reaction mixture was stirred at reflux temperature for 1 hr,
 20 concentrated and crystallized with ether to give 1-methyl-2-methylthio-2-imidazoline (1.1 g, 100%).

MS found for C₅H₁₀N₂S (M+H)⁺: 131.

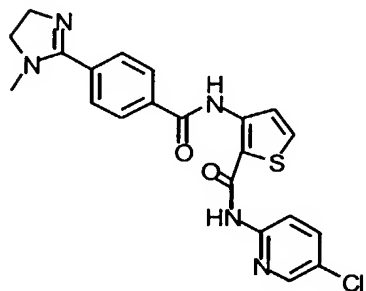
Step 2: A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (74 mg, 0.195 mmol), 1-methyl-2-methylthio-2-imidazoline (25 mg, 0.195 mmol), NEt₃ (2 mL) and pyridine (5 mL) was stirred at 80 °C overnight, concentrated and HPLC (C18 reversed phase)eluting
 25 with 0.1% TFA in H₂O/CH₃CN gave N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl} {4-[(1-methyl(2-imidazolin-2-

yl))amino]methyl}phenyl)carboxamide (52 mg, 65%). MS found for $C_{24}H_{23}ClN_6O_2$ (M+H)⁺: 463.

Example 163

5

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide



10

Preparation of methyl 3-[(4-cyanophenyl)carbonylamino]thiophene-2-carboxylate

A mixture of 4-cyanobenzoyl chloride (1.0500g, 6.4 mmol), methyl 3-aminothiophenecarboxylate (1.0000g, 6.4 mmol), and triethylamine (1 mL, 7.0 mmol) in dichloromethane was stirred at room temperature for 18 hours. The mixture was poured into a separatory funnel and washed by 1 N HCl. The organic layers were combined, dried over $MgSO_4$, concentrated in *vacuo*, and chromatographed through a silica gel column to give the title compound 1.6588 g (91%). ES-MS 287 (M+1).

20

Preparation of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}(4-cyanophenyl)carboxamide

A portion of 2-amino-5-chloropyridine (68.6 mg, 0.5 mmol) was treated with $AlMe_3$ (0.8 mL, 1.6 mmol), followed by adding the product from step A (160 mg, 0.5 mmol). The mixture was stirred at room temperature for 18 hours. The excess of $AlMe_3$ was killed by 1N HCl solution. The organic layers were combined, dried over $MgSO_4$, concentrated in *vacuo*, and chromatographed through a silica gel column to give the title compound 0.1528 g (80%). ES-MS 383 (M+1).

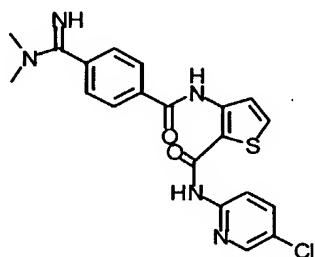
25

Preparation of Example 163.

- 5 A mixture of the product from step B (0.1528 g, 0.4 mmol) and EtOH saturated with HCl was stirred at room temperature for 18 hours. The solvent was removed by a rotovap. The crude oil was treated with 2 mL N-methylethylenediamine for 2 hours until the reaction was complete. Prep HPLC was used to purify the final product. It gave 0.1537 g (88%). ES-MS 440(M+1).

10 Example 164

{4-[(dimethylamino)iminomethyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carboxamide

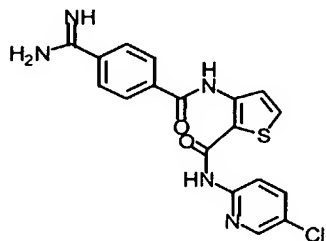


15

Example 164 was made by the procedure of Example 163. ES-MS 428(M+1).

Example 165

- 20 **4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]-3-thienyl}carbamoyl)benzenecarboxamidine**

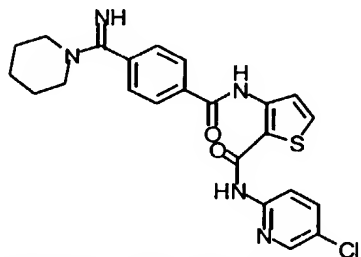


Example 165 was made by the procedure of Example 163. ES-MS 400(M+1).

Example 166

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopiperidylmethyl)-phenyl]carboxamide

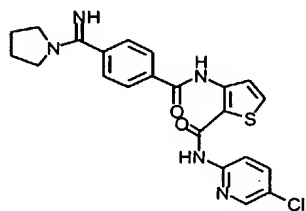
5



Example 166 was made by the procedure of Example 163. ES-MS 468(M+1).

Example 167

10 **N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopyrrolidylmethyl)-phenyl]carboxamide**

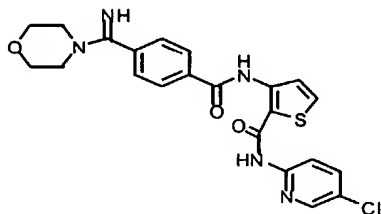


Example 167 was made by the procedure of Example 163. ES-MS 454(M+1).

Example 168

15

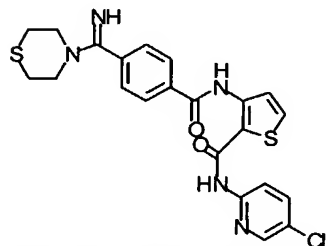
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminomorpholin-4-ylmethyl)phenyl]carboxamide



Example 168 was made by the procedure of Example 163. ES-MS 470(M+1).

Example 169

- 5 **N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carboxamide**

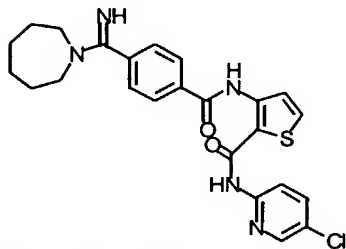


Example 169 was made by the procedure of Example 163. ES-MS 486(M+1).

Example 170

10

- [4-(azaperhydroepinyliminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carboxamide**

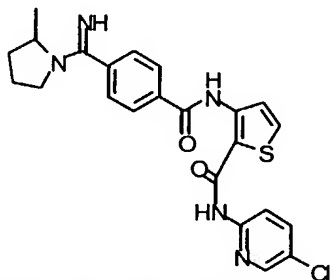


Example 170 was made by the procedure of Example 163. ES-MS 482(M+1).

15

Example 171

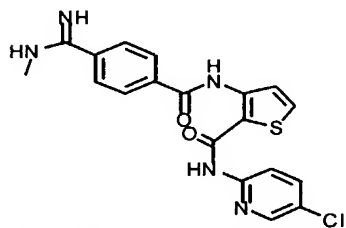
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}{4-[imino(2-methylpyrrolidinyl)methyl]phenyl}carboxamide



- 5 Example 171 was made by the procedure of Example 163. ES-MS 468(M+1).

Example 172

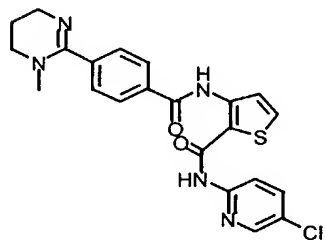
- 10 **N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}{4-[imino(methylamino)methyl]-phenyl}carboxamide**



Example 172 was made by the procedure of Example 163.

Example 173

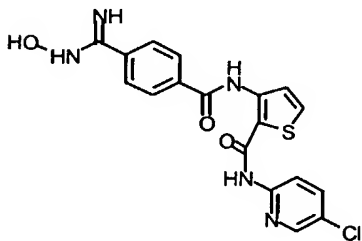
- 15 **N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}{4-(3-methyl(3,4,5,6-tetrahydropyrimidin-2-yl))phenyl}carboxamide**



Example 173 was made by the procedure of Example 163. ES-MS 414(M+1).

Example 174

- 5 **N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-((hydroxyamino)iminomethyl)-phenyl]carboxamide**

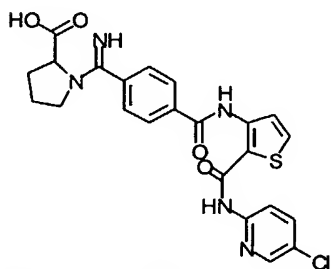


Example 174 was made by the procedure of Example 163. ES-MS 416(M+1).

10

Example 175

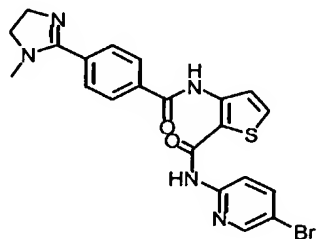
- 15 **1-{[4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carbamoyl)phenyl]-iminomethyl}pyrrolidine-2-carboxylic acid**



Example 175 was made by the procedure of Example 163. ES-MS 498(M+1).

Example 176

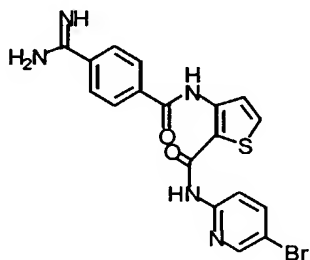
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide



- 5 Example 176 was made by the procedure of Example 163. ES-MS 484(M+1).

Example 177

4-(N-{2-[N-(5-bromo-2-pyridyl)carbamoyl]-3-thienyl}carbamoyl)benzenecarboxamidine



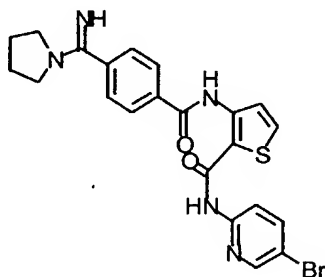
10

- Example 177 was made by the procedure of Example 163. ES-MS 444(M+1).

Example 178

N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopyrrolidinylmethyl)phenyl]carboxamide

15

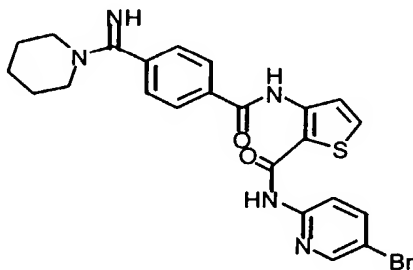


137

Example 178 was made by the procedure of Example 163. ES-MS 494(M+1).

Example 179

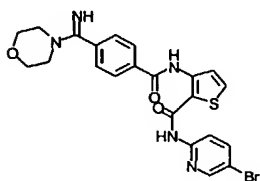
5 **N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopiperidylmethyl)phenyl]carboxamide**



Example 179 was made by the procedure of Example 163. ES-MS 512(M+1).

Example 180

10 **N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminomorpholin-4-ylmethyl)phenyl]carboxamide**



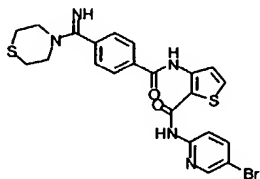
Example 180 was made by the procedure of Example 163. ES-MS 514(M+1).

15

Example 181

N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carboxamide

5

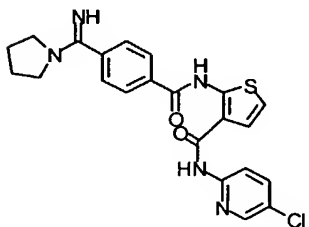


Example 181 was made by the procedure of Example 163. ES-MS 530(M+1).

Example 182

10

N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl)}[4-(iminopyrrolidinylmethyl)phenyl]carboxamide

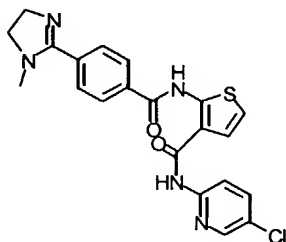


15 Example 182 was made by the procedure of Example 163. ES-MS 454(M+1).

Example 183

20

N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl)}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide

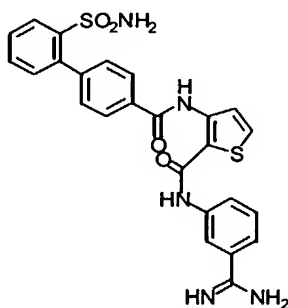


Example 183 was made by the procedure of Example 163. ES-MS 440(M+1).

Example 184

5

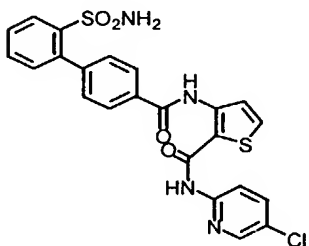
3-[(3-{[4-(2-sulfamoylphenyl)phenyl]carbonylamino}-2-thienyl)carbonylamino]benzenecarboxamide



- 10 Example 184 was made by the procedure of Example 163 (step A, B, C) followed by a final step of trifluoroacetic acid removal of the *t*-butyl group. 4-(2-{[(*tert*-butyl)amino]sulfonyl}phenyl)benzoyl chloride was used to replace 4-cyanobenzoyl chloride in Example 1. ES-MS 520(M+1).

15 Example 185

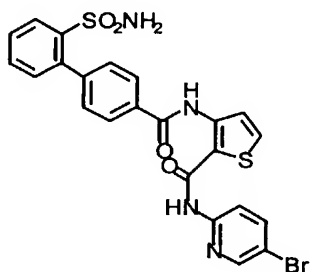
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(2-sulfamoylphenyl)phenyl]carboxamide



Example 185 was made by the procedure of Example 163 except using 4-(2-{{[(tert-butyl)amino]sulfonyl}phenyl}benzoyl chloride instead of 4-cyanobenzoyl chloride. ES-MS 513(M+1).

5 Example 186

N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(2-sulfamoylphenyl)phenyl]carboxamide

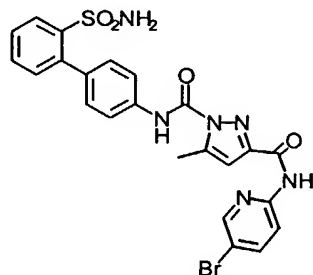


10

Example 186 was made by the procedure of Example 185. ES-MS 556(M+1).

Example 187

15 **N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl)5-methyl-pyrazolcarboxamide.**



20 Step 1: A solution of 2-amino-5-bromopyridine (0.200 g, 1.16 mmol 1.0 equiv), in 5 mls of methylene chloride, under argon, was treated with trimethylaluminum (0.312 mL, 2.0N in hexanes, 4.0 equiv) at room temperature for 30 min. To the solution was added ethyl-3-methylpyrazole-5-carboxylate (0.356 g, 2.0 equiv). After 4hrs, the volatile was evaporated, and the residue was redissolved into EtOAc, washed with

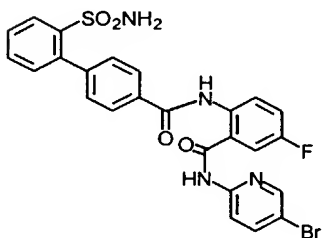
0.5N HCl, 0.2 N K₂CO₃, and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, evaporated and purified via flash chromatography on silica gel to give N-(5-bromo-2-pyridinyl)-(3-methyl)5-pyrazolecarboxamide (0.160 g, 49%). MS found for C₁₀H₉BrN₄O (M+H)⁺: 281, 283.

5

Step 2: A solution of N-(5-bromo-2-pyridinyl)-(3-methyl)5-pyrazolecarboxamide (0.060 g, 0.213 mmol, 1.0 equiv) in 2 mL of acetonitrile was treated with triphosgene (0.063 g, 1.0 equiv) at room temperature for 5min under argon. To the solution was added 4-[(2-t-butylaminosulfonyl)phenyl]phenylamine (0.071 g, 1.1 equiv) After 1 hr, the volatile was evaporated and the residue was redissolved into EtOAc, washed with 0.5N HCl, 0.2 N K₂CO₃, and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, evaporated, purified via flash chromatography on silica gel and then reacted in 2 mL of trifluoroacetic acid for 16 hrs at room temperature. TFA was then evaporated and the residue was redissolved into EtOAc, washed with 0.5N HCl, 0.2 N K₂CO₃, and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, evaporated, and triturated with diethyl ether to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylaminocarbonyl)5-methyl-pyrazolcarboxamide (0.0024 g, 2%). MS found for C₂₃H₁₉BrN₆O₄S (M+H)⁺: 555, 557.

20 Example 188

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarboxylamino)-5-fluorophenylcarboxamide.



25

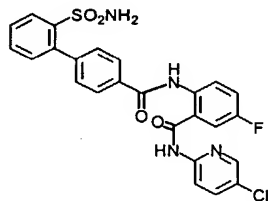
Step 1: A solution of 5-fluoro-2-nitrobenzoic acid (10.0 g, 54 mmol, 1.0 equiv), 2-amino-5-bromopyridine (12.2 g, 1.3 equiv), in 80 mL of pyridine was treated with phosphorous oxychloride (25.3 g, 3.0 equiv) for 30 min. The volatile was evaporated

and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO₃ and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, and evaporated. The volatile was evaporated, and the product was triturated with diethyl ether to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (12.5 g, 68%). MS found for C₁₂H₇BrFN₃O₃ (M+H)⁺: 340, 342.

Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (2.0 g, 5.88 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with SnCl₂·2H₂O (5.90 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous NaHCO₃ and 1N NaOH. The organic layer was dried over MgSO₄, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (1.79 g, 98%). MS found for C₁₂H₉BrFN₃O (M+H)⁺: 310, 312.

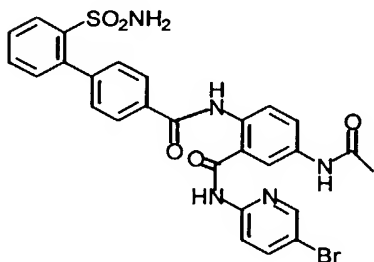
Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.310 g, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (0.430 g, 1.3 equiv), pyridine (2 mL) in 10 mL of dichloromethane was stirred at rt overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO₃ and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was triturated with diethyl ether, and then with chloroform to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)-5-fluorophenylcarboxamide (120 mg, 21%). MS found for C₂₅H₁₈BrFN₄O₄S (M+H)⁺: 569, 571.

Example 189

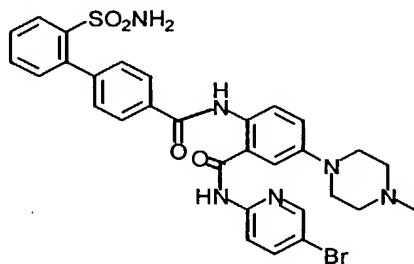


This compound is prepared according to the procedure described in example 2 with the exception of using zinc in acetic acid to reduce nitro-intermediate in step 2. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN. MS found for C₂₅H₁₈ClFN₄O₄S (M+H)⁺: 525, 527.

5

Example 190

10 This compound is prepared according to the procedure described in example 2 with the exception of using 5-acetamido-2-nitrobenzoic acid as the starting material in step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN MS found for C₂₇H₂₂BrN₅O₅S (M+H)⁺: 608, 610.

Example 191

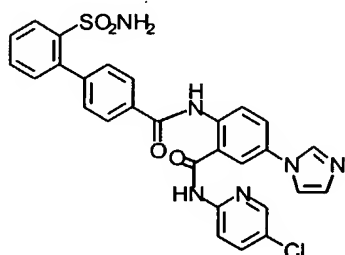
15

This compound is prepared according to the procedure described in example 2 with the exception of the following step 1b performed on the nitro-intermediate from step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN MS found for C₃₀H₂₉BrN₆O₄S (M+H)⁺: 649, 651.

20

Step 1b: A mixture of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (0.68 g, 2 mmol, 1.0 equiv), N-methylpiperazine (0.60 g, 3 equiv), and Cs₂CO₃ (1.30 g, 2 equiv) in 5 mL of dimethylformamide was stirred at 90°C overnight. Ethyl acetate was added and washed with H₂O. The organic layer was dried over Na₂SO₄, filtered, evaporated, purified via flash chromatography on silica gel to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-(4-N-methylpiperazine)phenylcarboxamide (0.54g, 65%). MS found for C₁₇H₁₈BrN₅O₃ (M+H)⁺: 419, 421.

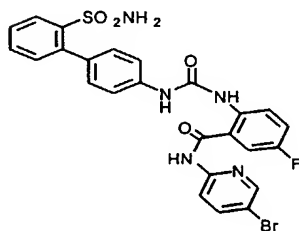
Example 192



This compound is prepared according to the procedure described in example 5. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN MS found for C₂₈H₂₁ClN₆O₄S (M+H)⁺: 573, 575.

Example 193

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonylamino)-5-fluorophenylcarboxamide.

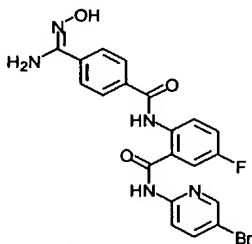


Step 3: A mixture of 4-[(2-t-butylaminosulfonyl)phenyl]phenylamine (0.180 g, 1.2 equiv), N,N'-disuccinimidyl carbonate (0.154 g, 1.2 equiv), 4-methylmorpholine (0.5

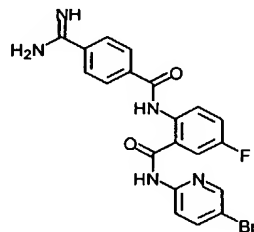
mL) in 10 mL of acetonitrile was stirred at rt for 30 min. N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.155 g, 0.5 mmol, 1.0 equiv) was added and the solution was stirred at rt for 3 hrs. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO₃ and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylaminocarbonylamino)-5-fluorophenylcarboxamide (0.053 g, 18%). MS found for C₂₅H₁₉BrFN₅O₄S (M+H)⁺: 584, 586.

Examples 194-195

15 N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenylcarboxamide.



Example 194



Example 195

Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)5-fluorophenylcarboxamide (1.24 g, 4 mmol, 1.0 equiv), 4-cyano benzoyl chloride (0.792 g, equiv), and pyridine (3 mL) in 15 mL of dichloromethane was stirred at rt overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO₃ and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.14 g, 65%). MS found for C₂₀H₁₂BrFN₄O₂ (M+H)⁺: 439, 441.

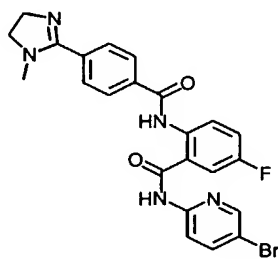
Step 2: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.12 g, 2.56 mmol, 1.0 equiv), hydroxylamine-HCl (0.213 g, 1.2 equiv), and triethylamine (1 mL) in 15 mL of ethyl alcohol was stirred at 50°C

overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO₃ and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (compound Example 194) (0.84 g, 70%). One third of this material was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to yield 0.20 grams (71%). MS found for C₂₀H₁₅BrFN₅O₃ (M+H)⁺: 472, 474.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (0.56 g, 1.19 mmol, 1.0 equiv) and zinc dust (0.39 g, 5.0 equiv), in 10 mL of acetic acid was stirred at rt for 45 min. The volatile was filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN give N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenyl-carboxamide (compound Example 195) (0.24 g, 44%). MS found for C₂₀H₁₅BrFN₅O₂ (M+H)⁺: 456, 458.

Example 196

N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide.



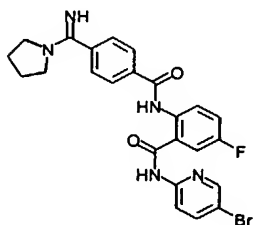
Step 1: A stream of HCl(g) was bubbled through a 0°C solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.0 g, 2.3 mmol) in 30 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. One-fifth of the resulting residue was treated with (2-aminoethyl)methylamine (0.10 g) in 10 ml methanol at rt overnight. The solvent was removed at reduced pressure and the crude product was purified by HPLC (C18

reversed phase) eluting with 0.5% TFA in H₂O/CH₃CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide (0.082 g, 37%). MS found for C₂₃H₁₉BrFN₅O₂ (M+H)⁺: 496, 498.

5

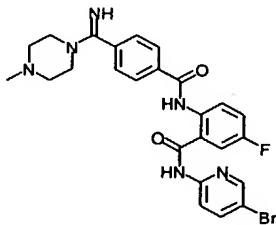
Examples 197-267

The following compounds were prepared generally according to the procedure described in Example 196.



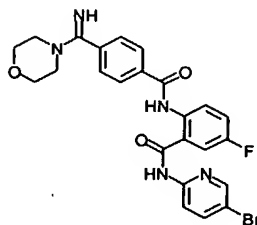
MS (M+H):
510, 512

Example 197



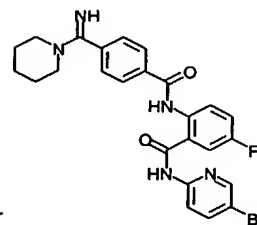
MS (M+H):
539, 541

Example 198



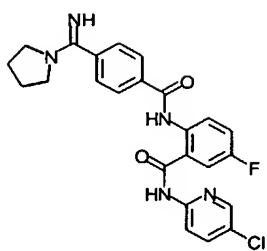
MS (M+H):
526, 528

Example 199



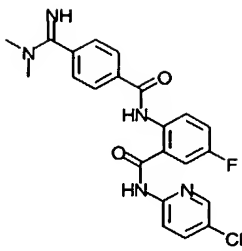
MS (M+H):
524, 526

Example 200



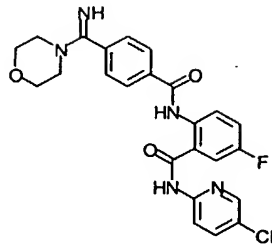
MS (M+H):
466, 468

Example 201



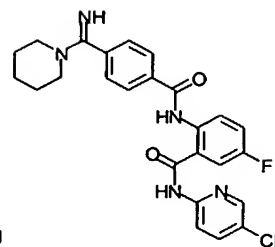
MS (M+H):
440, 442

Example 202



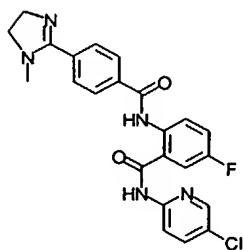
MS (M+H):
482, 484

Example 203



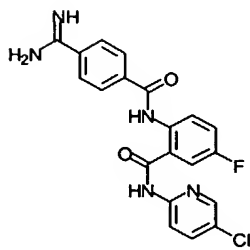
MS (M+H):
480, 482

Example 204



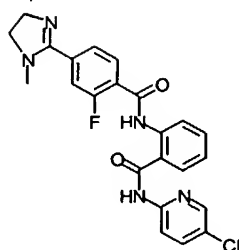
MS (M+H):
452, 454

Example 205



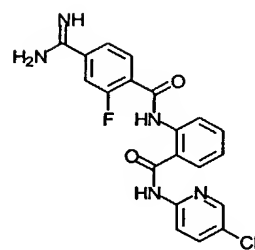
MS (M+H):
412, 414

Example 206



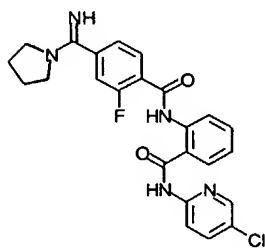
MS (M+H):
452, 454

Example 207



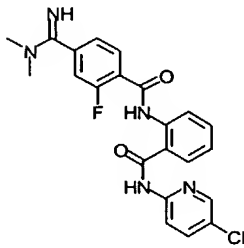
MS (M+H):
412, 414

Example 208



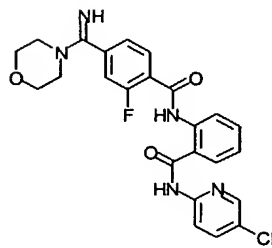
MS (M+H):
466, 468

Example 209



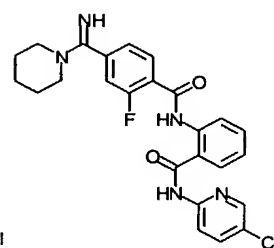
MS (M+H):
440, 442

Example 210



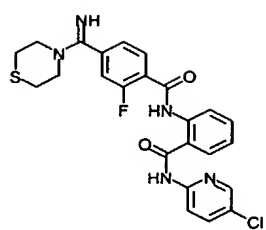
MS (M+H):
482, 484

Example 211

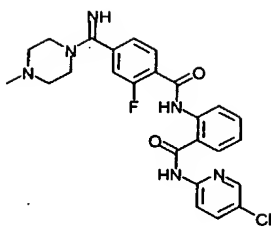


MS (M+H):
480, 482

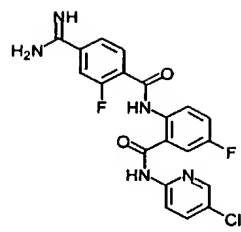
Example 212



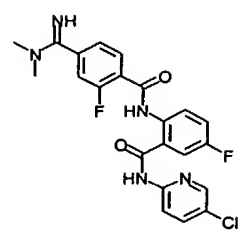
MS (M+H):
498, 500



MS (M+H):
495, 497



MS (M+H):
430, 432



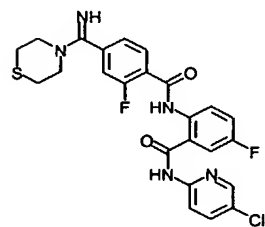
MS (M+H):
458, 460

Example 213

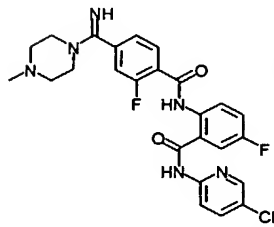
Example 214

Example 215

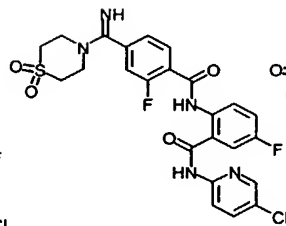
Example 216



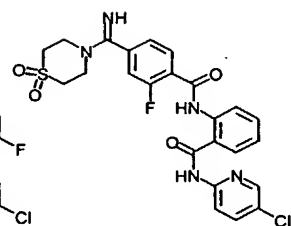
MS (M+H):
516, 518



MS (M+H):
513, 515



MS (M+H):
548, 550



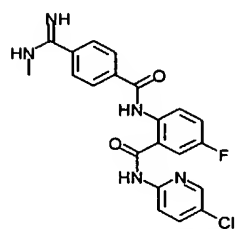
MS (M+H):
530, 532

Example 217

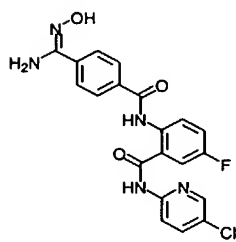
Example 218

Example 219

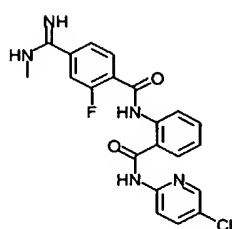
Example 220



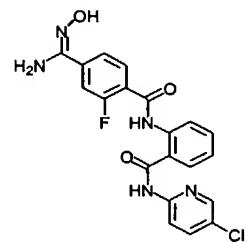
MS (M+H):
426, 428



MS (M+H):
428, 430



MS (M+H):
426, 428



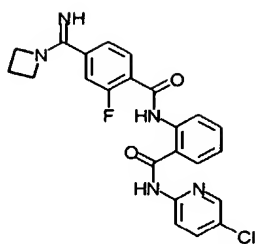
MS (M+H):
428, 430

Example 221

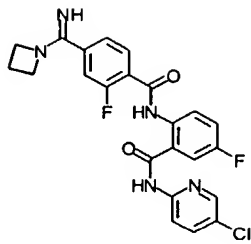
Example 222

Example 223

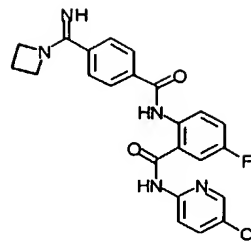
Example 224



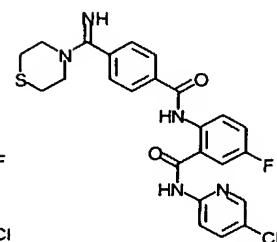
MS (M+H):
452, 454



MS (M+H):
470, 472



MS (M+H):
452, 454



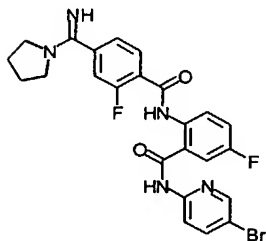
MS (M+H):
498, 500

Example 225

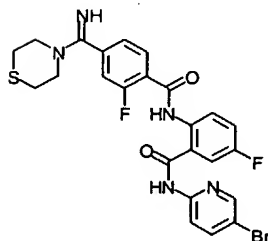
Example 226

Example 227

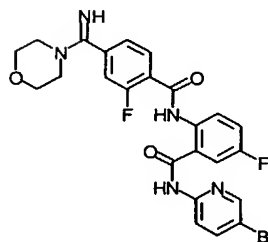
Example 228



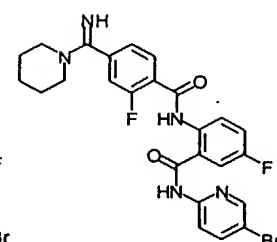
MS (M+H):
528, 530



MS (M+H):
560, 562



MS (M+H):
544, 546



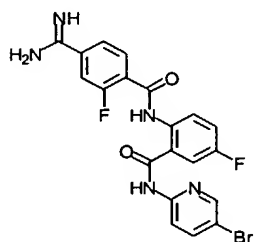
MS (M+H):
542, 544

Example 229

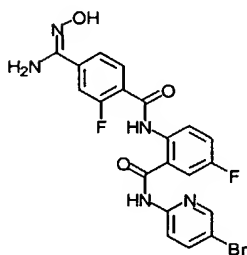
Example 230

Example 231

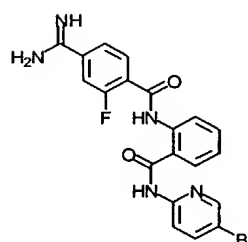
Example 232



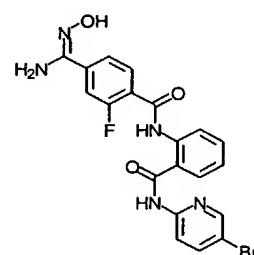
MS (M+H):
474, 476



MS (M+H):
490, 492



MS (M+H):
456, 458



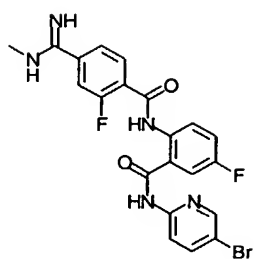
MS (M+H):
472, 474

Example 233

Example 234

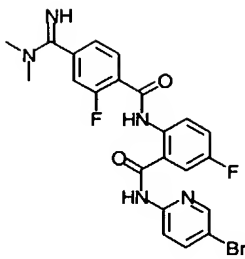
Example 235

Example 236



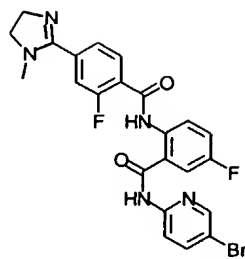
MS (M+H):
488, 490

Example 237



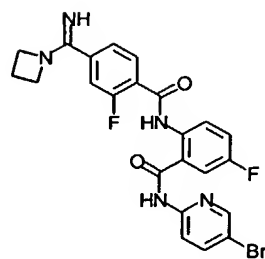
MS (M+H):
502, 504

Example 238



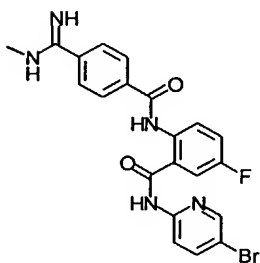
MS (M+H):
514, 516

Example 239



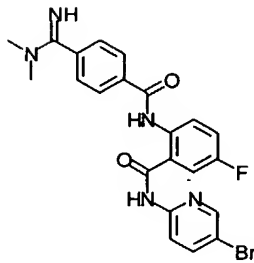
MS (M+H):
514, 516

Example 240



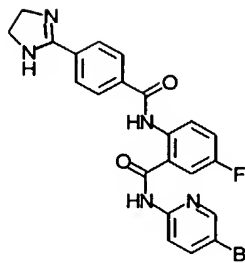
MS (M+H):
470, 472

Example 241



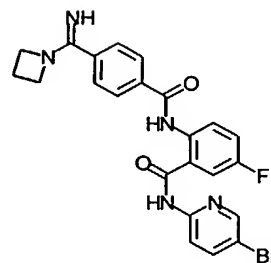
MS (M+H):
484, 486

Example 242



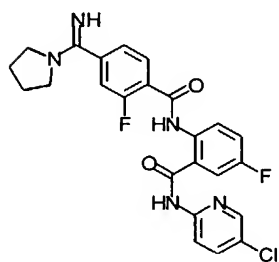
MS (M+H):
482, 484

Example 243



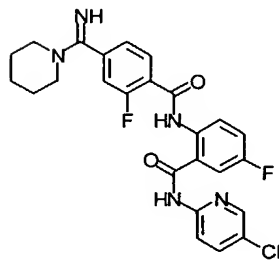
MS (M+H):
496, 498

Example 244



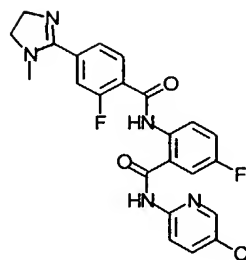
MS (M+H):
484, 486

Example 245



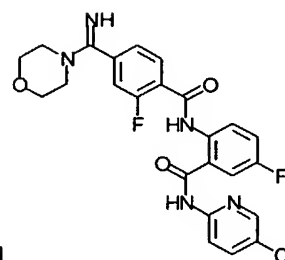
MS (M+H):
498, 500

Example 246



MS (M+H):
470, 472

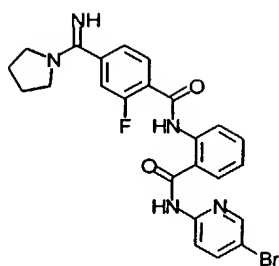
Example 247



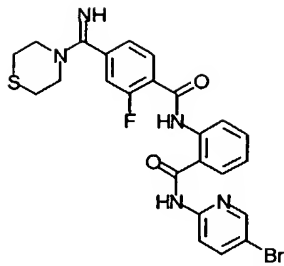
MS (M+H):
500, 502

Example 248

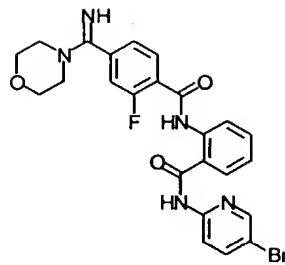
152



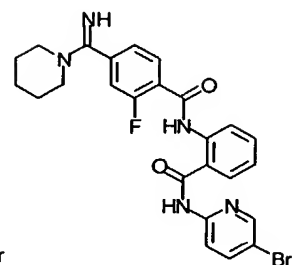
MS (M+H):
510, 512

Example 249

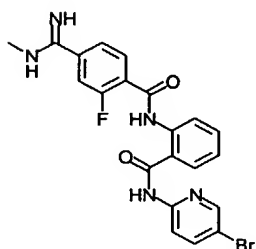
MS (M+H):
542, 544

Example 250

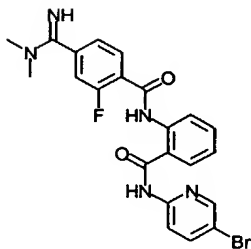
MS (M+H):
526, 528

Example 251

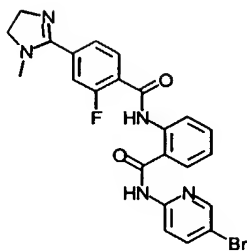
MS (M+H):
524, 526

Example 252

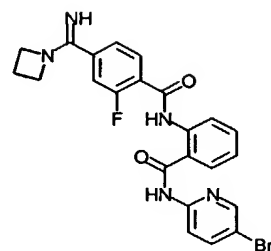
MS (M+H):
470, 472

Example 253

MS (M+H):
484, 486

Example 254

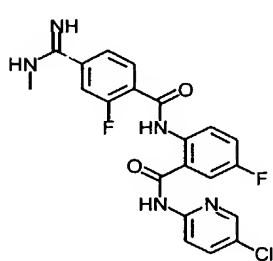
MS (M+H):
496, 498

Example 255

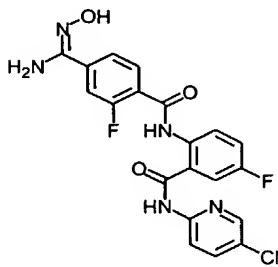
MS (M+H):
496, 498

Example 256

5



MS (M+H):
444, 446

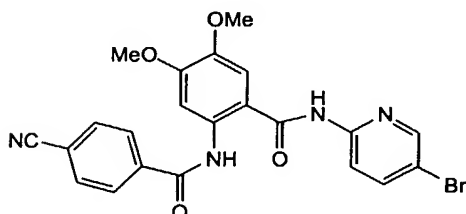
Example 257

MS (M+H):
446, 448

Example 258

Example 259**N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4,5-dimethoxyphenyl}(4-cyanophenyl)carboxamide**

5



To a solution of 4,5-dimethoxy-2-nitrobenzoic acid (2.2gm, 10mmol) and 2-amino-5-bromopyridine (2.4gm, 14mmol) in anhydrous pyridine (50mL) at 0°C was added POCl₃ (1.9mL, 20mmol). After stirring at room temperature for 30min, the reaction was complete. The mixture was concentrated and diluted with EtOAc (200mL). The organic solution was washed with brine, dried and evaporated to give intermediate compound 1 (3.0gm, 80%). MS found for C₁₄H₁₂BrN₃O₅ (M+H)⁺: 382.00, 383.95.

A mixture of intermediate compound 1 (320mg, 0.83mmol) and SnCl₂·2H₂O (900mg, 4.0mmol) in EtOAc (10mL) was refluxed for 1 hour. Reduction completed. The solid was filtered through a celite bed. The filtrate was diluted with EtOAc (50mL), and the red solution was washed with 1N aq. NaOH solution (x3) and brine, dried and evaporated to give intermediate compound 2 (230mg, 78%). MS found for C₁₄H₁₄BrN₃O₃ (M+H)⁺: 352.00, 354.05.

20

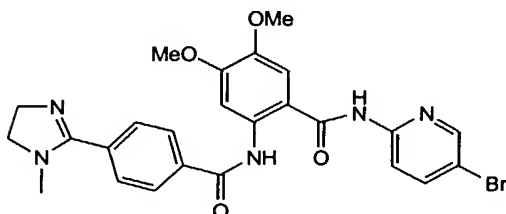
To a solution of intermediate compound 2 (200mg, 0.57mmol) in a mixture of pyridine (3mL) and DCM (10mL) was added 4-cyanobenzoyl chloride (140mg, 0.85mmol). Precipitate formed immediately and the reaction was complete. The solid was collected by filtration and washed with DCM. After drying in vacuo, the titled compound was obtained as a yellow solid in 70% yield (190mg). MS found for C₂₂H₁₇BrN₄O₄ (M+H)⁺: 481.00, 483.00.

25

Example 260

(4,5-dimethoxy-2-{{4-(1-methyl(2-imidazolin-2-yl))phenyl}carbonylamino}phenyl)-N-(5-bromo(2-pyridyl))carboxamide

5



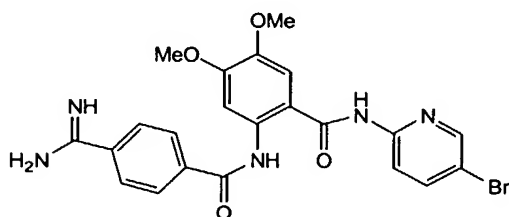
To a solution of compound obtained in Example 259 (100mg, 0.20mmol) in 10% Et₃N/pyridine (10mL) at 0°C was bubbled dry H₂S gas to saturation. The mixture was stirred at ambient temperatures overnight, and the conversion was complete. The solvent was removed to dryness, and the residue was suspended in anhydrous acetone (10mL), followed by addition of MeI (1mL). The reaction mixture was refluxed for 1 hour. The solvent was removed by rotary evaporation. To the residue was added anhydrous MeOH (10mL) and N-methylethylenediamine (1mL). The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give the title compound. MS found for C₂₅H₂₄BrN₅O₄ (M+H)⁺: 538.1, 540.1.

15

Example 261

4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4,5-dimethoxyphenyl}carbamoyl)-benzenecarboxamide

20

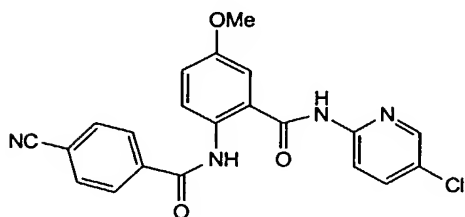


The title compound was obtained from the Example 259 compound according to the procedure described in Example 2. MS found for C₂₂H₂₀BrN₅O₄ (M+H)⁺: 498.1, 500.0.

25

Example 262

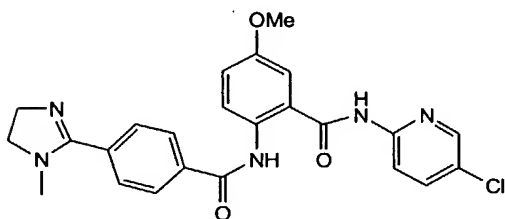
5 **N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}-carboxamide**



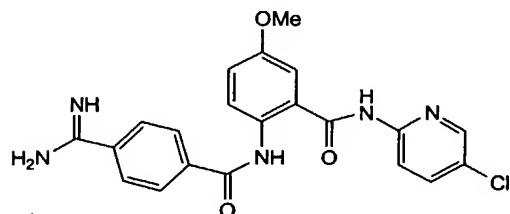
This compound was obtained from 5-methoxy-2-nitrobenzoic acid and 2-amino-5-chloro-pyridine according to the procedure described in Example 259. MS found for
10 $C_{21}H_{15}ClN_4O_3$ (M+H)⁺: 407.0.

Example 263

15 **N-(5-chloro(2-pyridyl))(5-methoxy-2-[[4-(1-methyl(2-imidazolin-2-yl))phenyl]-carbonylamino]phenyl)carboxamide**



To the suspension of the compound Example 262 (100mg) in a mixture of anhydrous MeOH (5mL) and EtOAc (5mL) at 0°C was bubbled anhydrous HCl gas to saturation.
20 The mixture was stirred at ambient temperatures overnight. The conversion completed. The solvent was evaporated to dryness. The residue was dissolved in anhydrous MeOH (10mL), followed by addition of N-methylethylenediamine (1mL). The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give the title compound 263. MS found for $C_{24}H_{22}ClN_5O_3$
25 (M+H)⁺: 464.

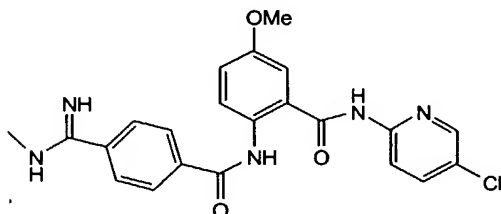
Example 264**4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methoxyphenyl}carbamoyl)benzene-carboxamidine**

5

The title compound was obtained from the Example 262 compound by procedures according to Example 262. MS found for $C_{21}H_{18}ClN_5O_3$ ($M+H$)⁺: 424.

Example 265

10

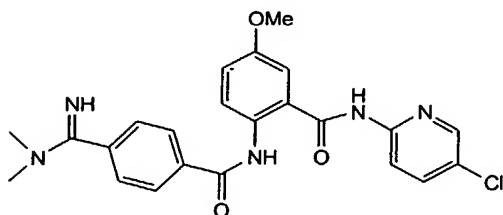
N-(5-chloro(2-pyridyl))[2-({4-[imino(methylamino)methyl]phenyl}carbonylamino)-5-methoxyphenyl]carboxamide

15

The title compound was obtained from N-(5-chloro(2-pyridyl)) {2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl} carboxamide and methylamine according to the procedure described in Example 262. MS found for $C_{22}H_{20}ClN_5O_3$ ($M+H$)⁺: 438.

Example 266

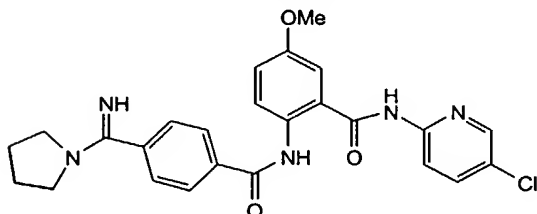
**[2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-
5 N-(5-chloro(2-pyridyl))carboxamide**



The title compound was obtained from N-(5-chloro(2-pyridyl)) {2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl} carboxamide and dimethylamine according to the procedure described in example 263. MS found for $C_{23}H_{22}ClN_5O_3$ (M+H)⁺: 452.

Example 267

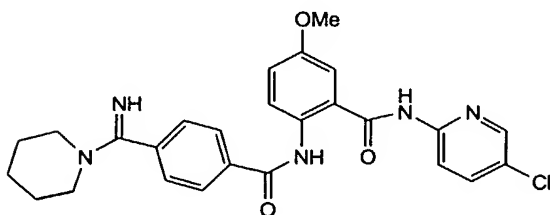
N-(5-chloro(2-pyridyl))(2-{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide



The title compound was obtained from N-(5-chloro(2-pyridyl)) {2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl} carboxamide and pyrrolidine according to the procedure described in Example 263. MS found for $C_{25}H_{24}ClN_5O_3$ (M+H)⁺: 478.

Example 268

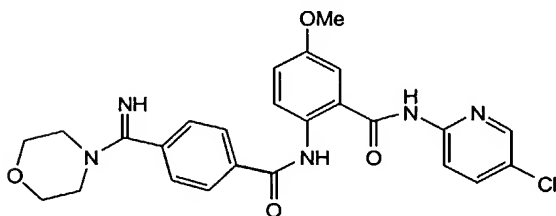
5 **N-(5-chloro(2-pyridyl))(2-{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide**



The title compound was obtained from N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide and piperidine
10 according to the procedure described in Example 263. MS found for $C_{26}H_{26}ClN_5O_3$ ($M+H$)⁺: 492.

Example 269

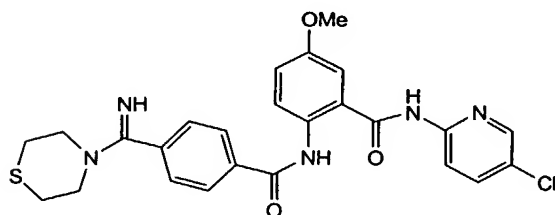
15 **N-(5-chloro(2-pyridyl))(2-{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide**



The title compound was obtained from N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide and morpholine
20 according to the procedure described in Example 263. MS found for $C_{25}H_{24}ClN_5O_4$ ($M+H$)⁺: 494.1.

Example 270

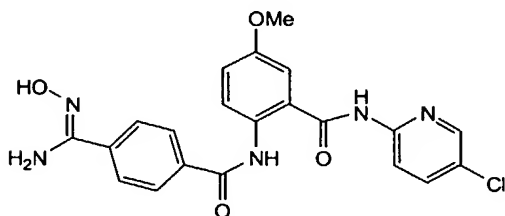
5 **N-(5-chloro(2-pyridyl))(2-{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide**



10 The title compound was obtained from N-(5-chloro(2-pyridyl))2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl} carboxamide and thiomorpholine according to the procedure described in Example 263. MS found for $C_{25}H_{24}ClN_5O_3S$ ($M+H$)⁺: 510.

Example 271

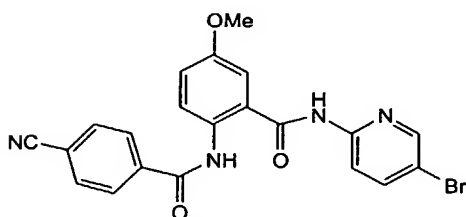
15 **(2-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide**



20 To a suspension of compound N-(5-chloro(2-pyridyl))2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl} carboxamide (150mg) in EtOH (10mL) was added hydroxyamine hydrochloride (80mg) and Et₃N (200μL). The mixture was stirred at 60°C overnight and the reaction was complete. The solvent was evaporated and the crude material was purified by RP-HPLC to give the title compound. MS found for $C_{21}H_{18}ClN_5O_4$ ($M+H$)⁺: 440.1.

Example 272

5 **N-(5-bromo(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide**

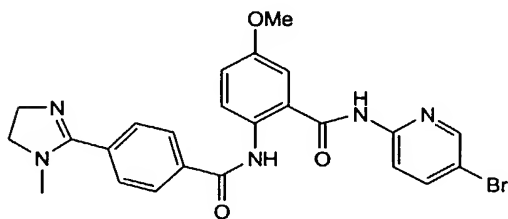


This compound was obtained from 5-methoxy-2-nitrobenzoic acid and 2-amino-5-bromo-pyridine according to the procedure described in Example 259. MS found for $C_{21}H_{15}BrN_4O_3$ ($M+H$)⁺: 451.00, 453.00.

10

Example 273

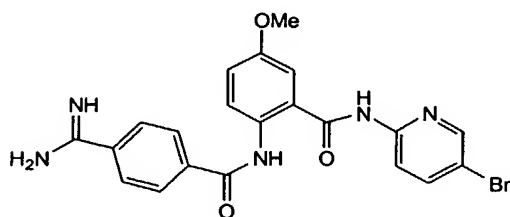
15 **N-(5-bromo(2-pyridyl))(5-methoxy-2-{[4-(1-methyl(2-imidazolin-2-yl))phenyl]carbonylamino}phenyl)carboxamide**



The title compound was obtained according to the procedure described Example 263. MS found for $C_{24}H_{22}BrN_5O_3$ ($M+H$)⁺: 508, 510.

Example 274

4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4-
5 methoxyphenyl}carbamoyl)benzenecarboxamidine

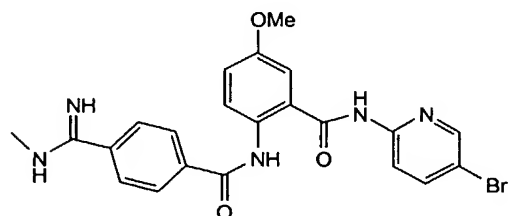


The title compound was obtained according to the procedure described in Example 263. MS found for $C_{21}H_{18}BrN_5O_3$ ($M+H$)⁺: 468.05, 470.00.

10

Example 275

N-(5-bromo(2-pyridyl))[2-({4-
[imino(methylamino)methyl]phenyl}carbonylamino)-5-
15 methoxyphenyl]carboxamide

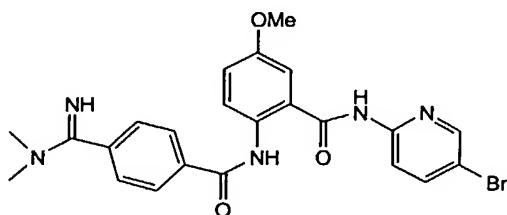


The title compound was obtained according to the procedure described in Example 263. MS found for $C_{22}H_{20}BrN_5O_3$ ($M+H$)⁺: 482, 484.

20

Example 276

5 **[2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-
N-(5-bromo(2-pyridyl))carboxamide**



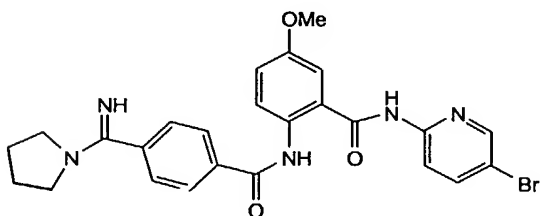
The title compound was obtained according to the procedure described in Example 263. MS found for $C_{23}H_{22}BrN_5O_3$ ($M+H$)⁺: 496.1, 498.1.

10

Example 277

**N-(5-chloro(2-pyridyl))(2-{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-
5-methoxyphenyl)carboxamide**

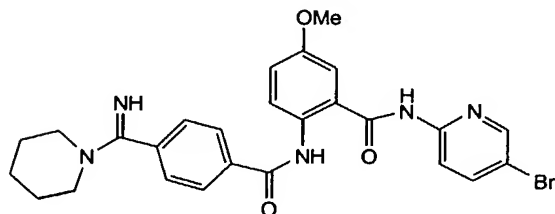
15



The title compound was obtained according to the procedure described in Example 263. MS found for $C_{25}H_{24}BrN_5O_3$ ($M+H$)⁺: 522, 524.

Example 278

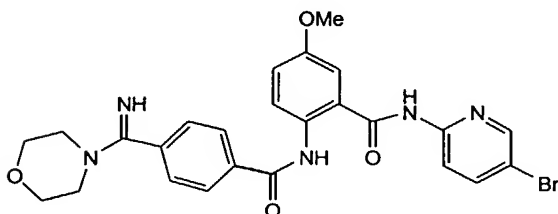
N-(N-(5-bromo(2-pyridyl))(2-{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide



The title compound was obtained according to the procedure described in Example 263. MS found for $C_{26}H_{26}BrN_5O_3$ ($M+H$)⁺: 536.1, 538.1.

Example 279

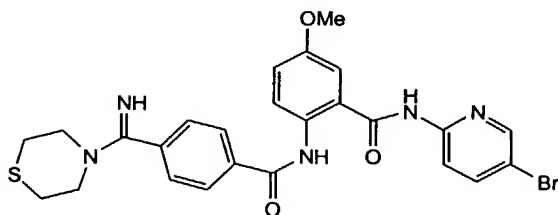
N-(5-bromo(2-pyridyl))(2-{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide



The title compound was obtained according to the procedure described in Example 263. MS found for $C_{25}H_{24}BrN_5O_4$ ($M+H$)⁺: 538.1, 540.1.

Example 280

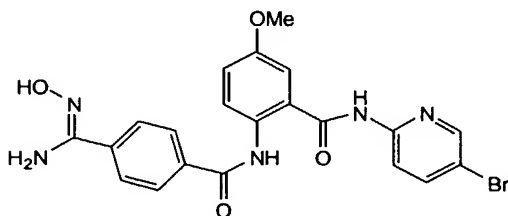
N-(5-bromo(2-pyridyl))(2-{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide



The title compound was obtained according to the procedure described in Example 263. MS found for $C_{25}H_{24}BrN_5O_3S$ ($M+H$)⁺: 554.1, 556.05.

Example 281

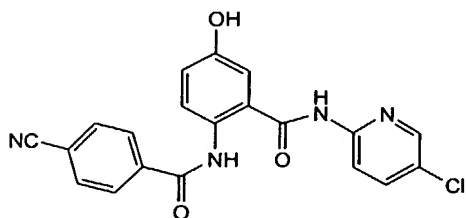
(2-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide



The title compound was obtained according to the procedure described in Example 270. MS found for $C_{21}H_{18}BrN_5O_4$ ($M+H$)⁺: 484.1, 486.0.

Example 282

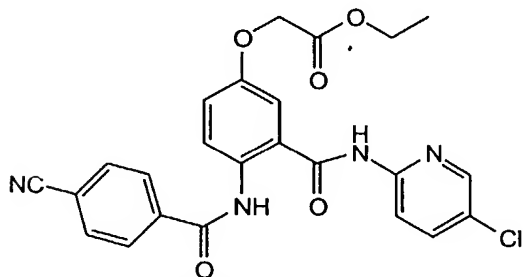
N-(5-chloro(2-pyridyl)){6-[(4-cyanophenyl)carbonylamino]-3-hydroxyphenyl}carboxamide



To a suspension of compound N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)-carbonylamino]-5-methoxyphenyl}carboxamide (500mg, 1.2mmol) in DCM (100mL) at -78°C was added BBr₃ (2mL). The mixture was stirred at ambient temperatures for 72 hours. The solid was collected by filtration and was washed by DCM and water, dried under vacuum. The filtrate was concentrated and extracted with EtOAc. The organic extract was washed with brine, dried and evaporated. The resulting solid was combined with the solid obtained from filtration to give the title compound. Total yield is 90% (430mg). MS found for C₂₀H₁₃ClN₄O₃ (M+H)⁺: 393.0.

Example 283

ethyl 2-{3-[N-(5-chloro(2-pyridyl))carbamoyl]-4-[(4-cyanophenyl)carbonylamino]-phenoxy}acetate



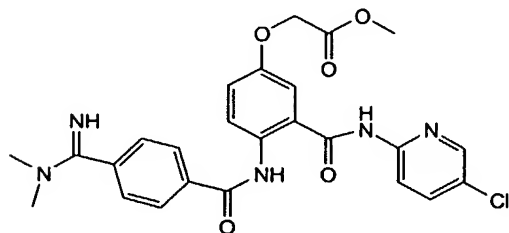
To a mixture of compound N-(5-chloro(2-pyridyl)){6-[(4-cyanophenyl)-carbonylamino]-3-hydroxyphenyl}carboxamide (50mg, 0.13mmol) and Cs₂CO₃

166

(83mg, 0.25mmol) in DMF (1mL) at room temperature was added ethyl bromoacetate (15μL, 0.13mmol). The mixture was stirred for 1 hour before diluted with EtOAc (20mL) and water (10mL). The organic layer was washed with brine dried and evaporated to give 70mg of the crude compound, which was used without farther
5 purification. MS found for $C_{24}H_{19}ClN_4O_5$ ($M+H$)⁺: 479.0.

Example 284

methyl 2-[4-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-3-[N-(5-chloro(2-pyridyl))carbamoyl]phenoxy]acetate
10

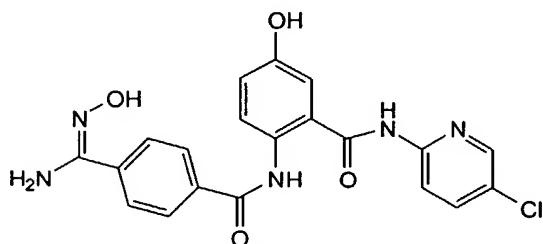


The title compound was obtained according to the procedure described Example 263.
MS found for $C_{25}H_{24}ClN_5O_5$ ($M+H$)⁺: 510.1.

15

Example 285

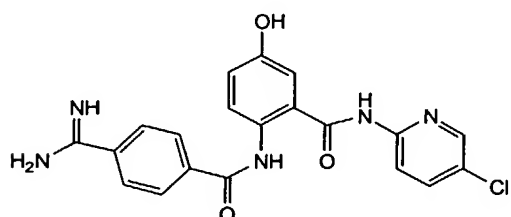
(6-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-3-hydroxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide
20



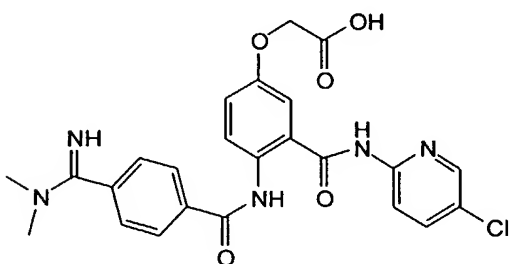
The title compound was obtained according to the procedure described in Example 270. MS found for $C_{20}H_{16}ClN_5O_4$ ($M+Na$)⁺: 448.0.

Example 286**4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-hydroxyphenyl}carbamoyl)-benzenecarboxamidine**

5



The title compound was obtained according to the procedure described in Example 282. MS found for $C_{20}H_{16}ClN_5O_3$ (M+H)⁺: 410.1.

10 Example 287**4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-hydroxyphenyl}carbamoyl)-benzenecarboxamidine**

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To a solution of Example 284 (10mg) in MeOH (1mL) was added 50μL of 1N aq. LiOH solution. The mixture was stirred for 1 hour and purified by RP-HPLC to give the title compound. MS found for $C_{24}H_{22}ClN_5O_5$ (M+H)⁺: 496.

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Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description

of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

WHAT IS CLAIMED IS:

1. A compound of the following formula :



wherein:

5 A is selected from:

- (a) $\text{C}_1\text{-C}_6\text{-alkyl}$;
 - (b) $\text{C}_3\text{-C}_8\text{-cycloalkyl}$;
 - 10 (c) $-\text{N}(\text{R}^1, \text{R}^2), \text{N}(\text{R}^1, \text{R}^2)\text{-C}(=\text{NR}^3)\text{-}, \text{N}(\text{R}^1, \text{R}^2)\text{-C}(=\text{NR}^3)\text{-N}(\text{R}^4)\text{-}, \text{R}^1\text{-C}(=\text{NR}^3)\text{-}, \text{R}^1\text{-C}(=\text{NR}^3)\text{-N}(\text{R}^4)\text{-}$;
 - (d) phenyl, which is independently substituted with 0-2 R substituents;
 - 15 (e) naphthyl, which is independently substituted with 0-2 R substituents;
- and
- a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be
- 20 substituted with 0-2 R substituents;

R is selected from:

- H, halo, $-\text{CN}$, $-\text{CO}_2\text{R}^1$, $-\text{C}(=\text{O})\text{-N}(\text{R}^1, \text{R}^2)$, $-(\text{CH}_2)_m\text{-CO}_2\text{R}^1$, $-(\text{CH}_2)_m\text{-C}(=\text{O})\text{-N}(\text{R}^1, \text{R}^2)$, $-\text{NO}_2$, $-\text{SO}_2\text{N}(\text{R}^1, \text{R}^2)$, $-\text{SO}_2\text{R}^1$, $-(\text{CH}_2)_m\text{NR}^1\text{R}^2$, $-(\text{CH}_2)_m\text{-C}(=\text{NR}^3)\text{-R}^1$, $-(\text{CH}_2)_m\text{-C}(=\text{NR}^3)\text{-N}(\text{R}^1, \text{R}^2)$, $-(\text{CH}_2)_m\text{-N}(\text{R}^4)\text{-C}(=\text{NR}^3)\text{-N}(\text{R}^1, \text{R}^2)$, $-(\text{CH}_2)_m\text{NR}^1$ - group appended to a 3 to 6 membered heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S, $-\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, $-\text{C}_{0-4}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{CF}_3$, $-\text{OR}^2$, and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, $-\text{C}_1\text{-C}_4\text{-alkyl}$, $-\text{C}_{1-4}\text{alkyl-CN}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, $-\text{C}_{0-4}\text{alkylC}_{3-8}\text{cycloalkyl}$ and $-\text{NO}_2$;

m is an integer of 0-2;

R¹, R², R³ and R⁴ are independently selected from the group consisting of:

5 H, -OR⁵, -N(-R⁵, -R⁶), -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂; or

10

R¹ and R², or R² and R³ taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C₁-C₄-alkyl, -CN -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

15

20 R⁵ and R⁶ are independently selected from the group consisting of:

H, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂; or

25

R⁵ and R⁶ taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, -C₁-C₄-alkyl, -CN -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

30

35

Q is a member selected from the group consisting of:

a direct link, $-\text{CH}_2-$, $-\text{C}(=\text{O})-$, $-\text{O}-$, $-\text{N}(\text{R}^7)-$, $-\text{N}(\text{R}^7)\text{CH}_2-$, $-\text{CH}_2\text{N}(\text{R}^7)-$, $-\text{C}(=\text{NR}^7)-$, $-\text{C}(=\text{O})-\text{N}(\text{R}^7)-$, $-\text{N}(\text{R}^7)-\text{C}(=\text{O})-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{SO}_2-\text{N}(\text{R}^7)-$ and $-\text{N}(\text{R}^7)-\text{SO}_2-$;

5 R^7 is selected from:

H, $-\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, $-\text{C}_{0-4}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{0-4}\text{alkylphenyl}$ and $-\text{C}_{0-4}\text{alkylnaphthyl}$, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of
 10 halo, $-\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, $-\text{C}_{0-4}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{CN}$, and $-\text{NO}_2$;

D is a direct link or is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;
 15 (b) naphthyl, which is independently substituted with 0-2 R^{1a} substituents; and
 (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be
 20 substituted from 0-2 R^{1a} substituents;

R^{1a} is selected from:

halo, $-\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, $-\text{C}_{0-4}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{CN}$, $-\text{NO}_2$, $-(\text{CH}_2)_n\text{NR}^{2a}\text{R}^{3a}$, $-(\text{CH}_2)_n\text{CO}_2\text{R}^{2a}$, $-(\text{CH}_2)_n\text{CONR}^{2a}\text{R}^{3a}$,
 25 $-\text{SO}_2\text{NR}^{2a}\text{R}^{3a}$, $-\text{SO}_2\text{R}^{2a}$, $-\text{CF}_3$, $-\text{OR}^{2a}$, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of
 30 halo, $-\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, $-\text{C}_{0-4}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{CN}$ and $-\text{NO}_2$;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, $-\text{C}_{1-4}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, $-\text{C}_{0-4}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{0-4}\text{alkylphenyl}$ and $-\text{C}_{0-4}\text{alkylnaphthyl}$, wherein from 1-4
 35 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be

independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

5 n is an integer of 0-2;

E is a direct link or a member selected from the group consisting of:

-C₁₋₂-alkyl-, -O-, -S-, -SO-, -SO₂-, -C₀₋₁-alkyl-C(=O), -C₀₋₁-alkyl-C(=O)-N(-R⁸)-C₀₋₁-alkyl-, -C₀₋₁-alkyl-N(-R⁸)-C(=O)-C₀₋₁-alkyl-, -N(-R⁸)-C(=O)-N(-R⁸)- and -C₀₋₁-alkyl-N(-R⁸)-;

10

R⁸ is a member selected from the group consisting of:

H; -C₁₋₄-alkyl; -C₀₋₄-alkylaryl; -C₀₋₄-alkyl-heteroaryl; -C₁₋₄-alkyl-C(=O)-OH, -C₁₋₄-alkyl-C(=O)-O-C₁₋₄-alkyl, and -C₁₋₄-alkyl-C(=O)-N(-R^{2b}, -R^{3b});

15

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

H, -C₁₋₄-alkyl, -C₀₋₄-alkyl-aryl; -C₀₋₄-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

20

R^{1c} is a member selected from the group consisting of:

Halo; -C₁₋₄-alkyl; -CN, -NO₂; -C(=O)-N(-R^{2c}, -R^{3c}); -C(=O)-OR^{2c}; -(CH₂)_q-N(-R^{2c}, -R^{3c}); -SO₂-N(-R^{2c}, -R^{3c}); -SO₂R^{2c}; -CF₃ and -(CH₂)_q-OR^{2c};

25

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

H; -C₁₋₄-alkyl and -C₁₋₄-alkyl-aryl;

q is an integer of 0-2;

30

G is a member selected from the group consisting of:

(a) C₂-alkenyl or C₃₋₈-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein the -C₂-alkenyl or -C₃₋₈-cycloalkenyl are substituted with 0-4 R^{1d} groups;

35

- (b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;
- (c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,
- (d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

- H, halo; C_{1-6} -alkyl, carbocyclic aryl, -CN; -NO₂; -(CH₂)₀₋₆-NR^{2d}R^{3d};
 -SO₂NR^{2d}R^{3d}; -SO₂R^{2d}; -CF₃; -(CH₂)₀₋₆-OR^{2d}; -O-(CH₂)₁₋₆OR^{2d}; -O-(CH₂)₁₋₆-C(=O)-O-R^{2d};
 -O-(CH₂)₁₋₆-C(=O)-N(R^{2d},R^{3d}); -N(R^{5a})-(CH₂)₁₋₆-OR^{2d};
 -N(R^{5a})-(CH₂)₁₋₆-N(R^{2d},R^{3d}); -C(=O)-N(R^{2d},R^{3d});
 -N(R^{5a})-(CH₂)₁₋₆-C(=O)-N(R^{2d},R^{3d}); -N(-(CH₂)₁₋₆-OR^{2d})₂; -N(R^{5a})-(CH₂)₁₋₆-OR^{2d};
 -N(R^{5a})-C(=O)-R^{2d}; -N(R^{5a})-SO₂-R^{2d}; -(CH₂)₀₋₆-C(=O)-O-R^{2d}; -(CH₂)₀₋₆-C(=O)-N(R^{2d},R^{3d});
 -(CH₂)₀₋₆-C(=NR^{2d})-N(R^{3d},R^{4d}); -(CH₂)₀₋₆-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d}); a -(CH₂)₀₋₆-N(R^{3d})C_{5,6} membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a -(CH₂)₀₋₆-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{5a} , R^{2d} , R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

- H, C_{1-6} -alkyl and C_{1-6} -alkylaryl, -CN; -NO₂; carbocyclic aryl, -CN; -NO₂; or

R^{2d} and R^{3d} taken together with the N atoms they are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

- 5 J is a direct link or is a member selected from the group consisting of:
 $-N(-R^9)-C(=O)-$; $-C(=O)-N(-R^9)-$; $-O-$; $-S-$; $-SO-$; $-SO_2-$; $-CH_2-$; $-N(-R^9)-$; and
 $-N(-R^9)-SO_2-$;

R^9 is a member selected from the group consisting of:

- 10 H; $-C_{1-4}$ -alkyl; $-C_{0-4}$ -alkyl-carbocyclic aryl; $-(CH_2)_{0-4}$ -5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S; $-(CH_2)_{1-6}-C(=O)-O-C_{1-4}$ -alkyl; and $-(CH_2)_1-$
 $-C(=O)-N(R^{6a}, R^{6b})$;

- 15 R^{6a} and R^{6b} are each a member independently selected from the group consisting of:
H and $-C_{1-6}$ -alkyl;

X is a member selected from the group consisting of:

- (a) phenyl substituted with 0-3 R^{1e} groups;
20 (b) naphthyl substituted with 0-3 R^{1e} groups and
(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and
25 (d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

30

R^{1e} is a member independently selected from the group consisting of:

- Halo; CF_3 ; $-C_{1-4}$ -alkyl; carbocyclic aryl; $-C_{0-2}$ -alkyl-CN; $-O-R^{2e}$;
 $-C_{0-2}$ -alkyl- $C(=O)-O-R^{2e}$; $-C_{0-2}$ -alkyl- $C(=O)-N(R^{2e}, R^{3e})$; $-C_{0-2}$ -alkyl- NO_2 ;
 $-C_{0-2}$ -alkyl- $N(R^{2e}, R^{3e})$; $-C_{0-2}$ -alkyl- $SO_2-N(R^{2e}, R^{3e})$; $-C_{0-2}$ -alkyl- SO_2-R^{2e} ;
35 trihaloalkyl; $-O-C_{0-2}$ -alkyl- $O-R^{2e}$; $-C_{0-2}$ -alkyl- $O-R^{2e}$; $-O-C_{1-4}$ -alkyl-

$C(=O)-N(R^{2e}, R^{3e})$; $-O-C_{1-4}-alkyl-C(=O)-O-R^{2e}$; $-C_{0-2}-alkyl-N(R^{2e})-C(=O)-R^{3e}$;
 $-C_{0-2}-alkyl-N(-R^{2e})-SO_2-R^{3e}$; $-CH_2-N(R^{2e})-C(=O)-R^{3e}$; $-CH_2-N(R^{2e})-SO_2-R^{3e}$;
 $-(CH_2)_{0-6}-NR^{2e}R^{3e}$; $-C(=O)-N(R^{2e}, R^{3e})$; $-N(-(CH_2)_{1-6}-OR^{2e})_2$; $-N(R^{10})-(CH_2)_{1-6}-OR^{2e}$;
 $-N(R^{10})-C(=O)-R^{2e}$; $-N(R^{10})-SO_2-R^{2e}$; $-C(=N(R^{10}))-N(R^{2e}, R^{3e})$; and a
 5 $-(CH_2)_{0-6}$ -5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10} , R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

10 H; $-C_{1-4}-alkyl$; $-C_{0-2}-alkyl-O-R^{1g}$; $-C_{0-2}-alkyl-N(-R^{1g}, -R^{2g})$; $-C_{1-4}-alkyl-carbocyclic\ aryl$; $-C_{1-4}-alkyl-heterocyclic$; and R^{10} and R^{2e} , or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

15

R^{1g} and R^{2g} are independently a member selected from the group of:

H; halo; $-C_{1-4}-alkyl$, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; $-CN$; $-C(=O)-N(R^{3g})R^{4g}$; $-C(=O)-OR^{3g}$; $-NO_2$;
 $-(CH_2)_p-NR^{3g}R^{4g}$; $-SO_2NR^{3g}R^{4g}$; $-SO_2R^{3g}$; $-CF_3$; and $-(CH_2)_pOR^{3g}$;

20

p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; $-C_{1-4}-alkyl$ and $-C_{0-4}-alkyl-carbocyclic\ aryl$;

25

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

2. A compound of claim 1, wherein:

30 A is selected from:

(a) $C_1-C_6-alkyl$;

(b) $C_3-C_8-cycloalkyl$;

- (c) $-N(R^1, R^2)$, $N(R^1, R^2)-C(=NR^3)-$, $N(R^1, R^2)-C(=NR^3)-N(R^4)-$, $R^1-C(=NR^3)-$, $R^1-C(=NR^3)-N(R^4)-$;
- (d) phenyl, which is independently substituted with 0-2 R substituents;
- (e) naphthyl, which is independently substituted with 0-2 R substituents;
- and
- (f) monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substituents;

R is selected from:

- H, halo, $-CN$, $-CO_2R^1$, $-C(=O)-N(R^1, R^2)$, $-(CH_2)_m-CO_2R^1$, $-(CH_2)_m-C(=O)-N(R^1, R^2)$, $-NO_2$, $-SO_2N(R^1, R^2)$, $-SO_2R^1$, $-(CH_2)_mNR^1R^2$, $-(CH_2)_m-C(=NR^3)-R^1$, $-(CH_2)_m-C(=NR^3)-N(R^1, R^2)$, $-(CH_2)_m-N(R^4)-C(=NR^3)-N(R^1, R^2)$, $-(CH_2)_mNR^1$ - group attached to a 3-6 membered heterocyclic ring having from 1 to 3 heteroatoms selected from the group consisting of N, O and S, $-C_{1-4}alkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-C_{3-8}cycloalkyl$, $-C_{0-4}alkylC_{3-8}cycloalkyl$, $-CF_3$, $-OR^2$, and a 5-6 membered heterocyclic aromatic or partially saturated system, including imidazoline, containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of
- halo, -methyl, $-C_2-C_4-alkyl$, $-CN$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-C_{3-8}cycloalkyl$, $-C_{0-4}alkylC_{3-8}cycloalkyl$ and $-NO_2$;

m is an integer of 0-2;

- R^1 , R^2 , R^3 and R^4 are independently selected from the group consisting of:
- H, $-OR^5$, $-N(-R^5, -R^6)$, $-C_{1-4}alkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-C_{3-8}cycloalkyl$, $-C_{0-4}alkylC_{3-8}cycloalkyl$, $-C_{0-4}alkylphenyl$ and $-C_{0-4}alkylnaphthyl$, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group

consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂; or

5 R¹ and R², or R² and R³ taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C₁-C₄-alkyl, -CN -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

R⁵ and R⁶ are independently selected from the group consisting of:

15 H, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂; or

20 R⁵ and R⁶ taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C₁-C₄-alkyl, -CN -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

Q is a member selected from the group consisting of:

30 a direct link, -CH₂-, -C(=O)-, -O-, -NH-, -NMe-, -NHCH₂-, -NMeCH₂-, -CH₂NH-, -C(=NH)-, -C(=O)-NH-, -NH-C(=O)-, -CH₂NMe-, -C(=NMe)-;

D is a direct link or is a member selected from the group consisting of:

35 (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substituents; and

5 a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted from 0-2 R^{1a} substituents;

R^{1a} is selected from:

10 halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, -(CH₂)_nNR^{2a}R^{3a}, -(CH₂)_nCO₂R^{2a}, -(CH₂)_nCONR^{2a}R^{3a}, -SO₂NR^{2a}R^{3a}, -SO₂R^{2a}, -CF₃, -OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of

15 halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

R^{2a} and R^{3a} are independently selected from the group consisting of:

20 H, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -C₀₋₄alkylphenyl and -C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C₁₋₄alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₈cycloalkyl, -C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

25

n is an integer of 0-2;

E is a member selected from the group consisting of:

30 a direct link, -O-, -NH-, -CH₂NH-, -NHCH₂-, -NMe-, -NH-C(=O)-NH-, -C(=O)-NH-, -NH-C(=O)-;

G is a member selected from the group consisting of:

(a) a C₂-alkenyl group or a C₃₋₈-cycloalkenyl group, wherein the alkenyl group and cycloalkenyl group attachment points are the alkenyl carbon

atoms and wherein the C₂-alkenyl group or C₃₋₈-cycloalkenyl group is substituted with 0-4 R^{1d} groups;

- 5 (b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;
- (c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,
- 10 (d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

15

R^{1d} is a member selected from the group consisting of:

- H, halo; C₁₋₆-alkyl, carbocyclic aryl, -CN; -NO₂; -(CH₂)₀₋₆-NR^{2d}R^{3d},
 -SO₂NR^{2d}R^{3d}; -SO₂R^{2d}; -CF₃; -(CH₂)₀₋₆-OR^{2d}; -O-(CH₂)₁₋₆OR^{2d}; -O-(CH₂)₁₋₆-C(=O)-O-R^{2d};
 20 -O-(CH₂)₁₋₆-C(=O)-N(R^{2d},R^{3d}); -N(R^{5a})-(CH₂)₁₋₆-OR^{2d},
 -N(R^{5a})-(CH₂)₁₋₆-N(R^{2d},R^{3d}); -C(=O)-N(R^{2d},R^{3d});
 -N(R^{5a})-(CH₂)₁₋₆-C(=O)-N(R^{2d},R^{3d}); -N(-(CH₂)₁₋₆-OR^{2d})₂; -N(R^{5a})-(CH₂)₁₋₆-OR^{2d};
 -N(R^{5a})-C(=O)-R^{2d}; -N(R^{5a})-SO₂-R^{2d}; -(CH₂)₀₋₆-C(=O)-O-R^{2d}; -(CH₂)₀₋₆-C(=O)-N(R^{2d},R^{3d}); -(CH₂)₀₋₆-C(=NR^{2d})-N(R^{3d},R^{4d});
 25 -(CH₂)₀₋₆-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d}); and a -(CH₂)₀₋₆-N(R^{3d}) group which is attached via the nitrogen atom to a carbon atom of a 5 to 6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a -(CH₂)₀₋₆- group attached to a 5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring
 30 containing 1-4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

- 35 H, C₁₋₆-alkyl and C₁₋₆-alkylaryl, -CN; -NO₂; carbocyclic aryl, -CN; -NO₂; or

R^{2d} and R^{3d} taken together with the N atoms they are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

- 5 R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

J is a member selected from the group consisting of:

- 10 a direct link, -O-, -NH-, -NMe-, -C(=O)-NH-, -NH-C(=O)-;

X is a member selected from the group consisting of:

- (a) phenyl substituted with 0-3 R^{1e} groups;
- 15 (b) naphthyl substituted with 0-3 R^{1e} groups and
- (c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and
- 20 (d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

- 25 R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3 ; $-C_{1-4}$ -alkyl; carbocyclic aryl; $-C_{0-2}$ -alkyl-CN; $-O-R^{2e}$; $-C_{0-2}$ -alkyl-C(=O)-O- R^{2e} ; $-C_{0-2}$ -alkyl-C(=O)-N(R^{2e} , R^{3e}); $-C_{0-2}$ -alkyl-NO₂; $-C_{0-2}$ -alkyl-N(R^{2e} , R^{3e}); $-C_{0-2}$ -alkyl-SO₂-N(R^{2e} , R^{3e}); $-C_{0-2}$ -alkyl-SO₂- R^{2e} ; trihaloalkyl; $-O-C_{0-2}$ -alkyl-O- R^{2e} ; $-C_{0-2}$ -alkyl-O- R^{2e} ; $-O-C_{1-4}$ -alkyl-C(=O)-N(R^{2e} , R^{3e}); $-O-C_{1-4}$ -alkyl-C(=O)-O- R^{2e} ; $-C_{0-2}$ -alkyl-N(R^{2e})-C(=O)- R^{3e} ; $-C_{0-2}$ -alkyl-N(R^{2e})-SO₂- R^{3e} ; $-CH_2$ -N(R^{2e})-C(=O)- R^{3e} ; $-CH_2$ -N(R^{2e})-SO₂- R^{3e} ; $-(CH_2)_{0-6}$ -NR^{2e}R^{3e}; $-C(=O)$ -N(R^{2e} , R^{3e}); $-N(-(CH_2)_{1-6}-OR^{2e})_2$; $-N(R^{10})-(CH_2)_{1-6}-OR^{2e}$; $-N(R^{10})-C(=O)-R^{2e}$; $-N(R^{10})-SO_2-R^{2e}$; $-C(=N(R^{10}))$ -N(R^{2e} , R^{3e}); and a $-(CH_2)_{0-5}$ -6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

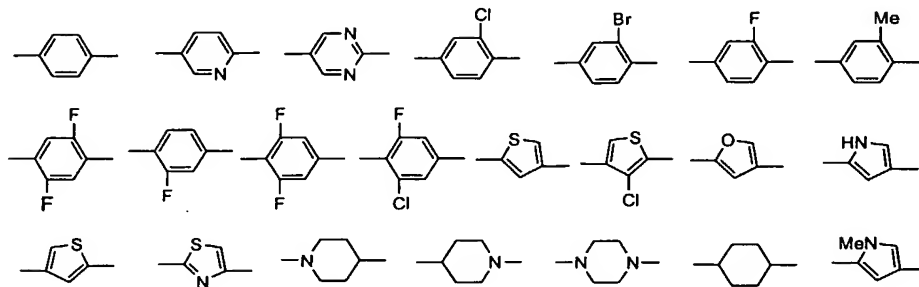
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R^{10} , R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

- 5 H; $-C_{1-4}$ -alkyl; $-C_{0-2}$ -alkyl-O- R^{1g} ; $-C_{0-2}$ -alkyl-N($-R^{1g}$, $-R^{2g}$); $-C_{1-4}$ -alkyl-carbocyclic aryl; $-C_{1-4}$ -alkyl-heterocyclic; and R^{10} and R^{2e} , or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;
- 10 R^{1g} and R^{2g} are independently a member selected from the group of:
 H; halo; $-C_{1-4}$ -alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; $-CN$; $-C(=O)-N(R^{3g}, R^{4g})$; $-C(=O)-OR^{3g}$; $-NO_2$; $-(CH_2)_p-NR^{3g}R^{4g}$; $-SO_2NR^{3g}R^{4g}$; $-SO_2R^{3g}$; $-CF_3$; and $-(CH_2)_pOR^{3g}$;
- 15 p is an integer of 0-2;
- R^{3g} and R^{4g} are each independently selected from the group consisting of:
 H; C_{1-4} -alkyl and $-C_{0-4}$ -alkyl-carbocyclic aryl;
- 20 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

D is a direct link or is a member selected from the group consisting of:

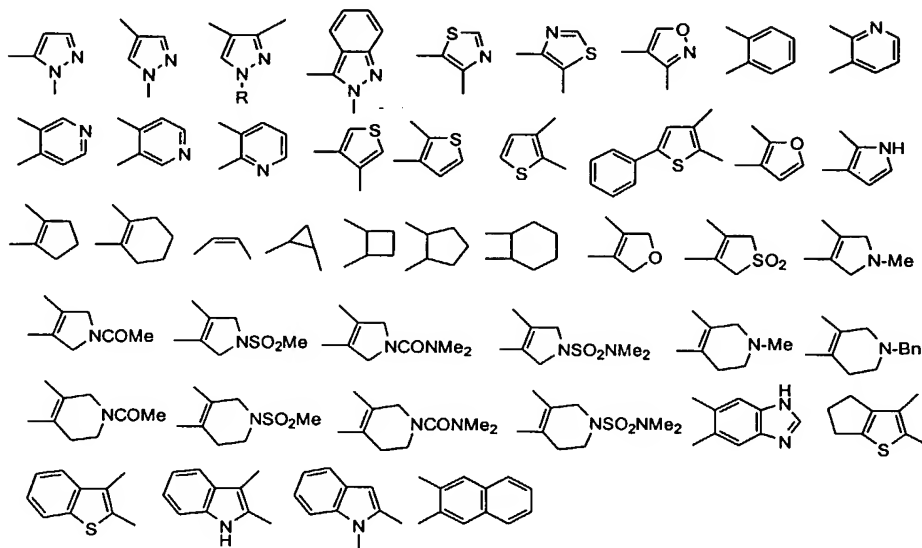


E is a member selected from the group consisting of:

a direct link, $-\text{CH}_2\text{NH}-$, $-\text{C}(=\text{O})-\text{NH}-$, $-\text{NH}-\text{C}(=\text{O})-$;

5

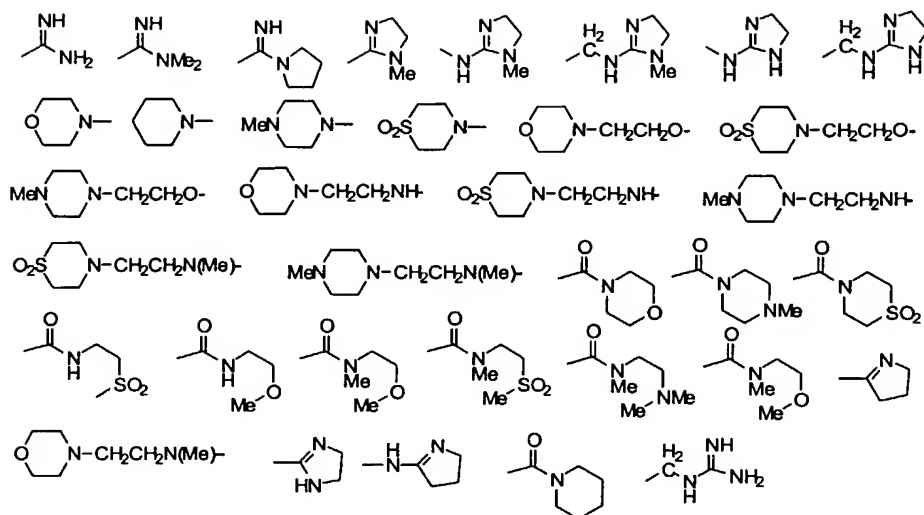
G is a member selected from the group consisting of:



10 G is substituted by 0-4 R^{1d} groups and each R^{1d} group is independently selected from the group consisting of:

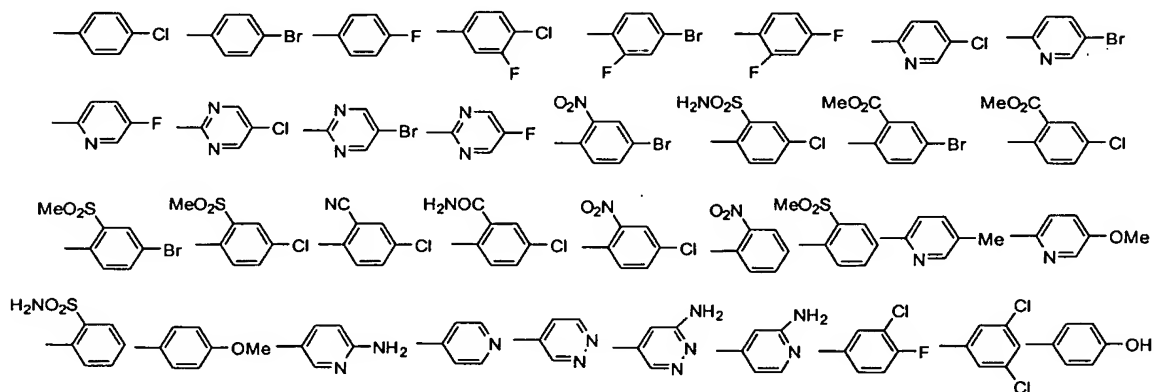
H, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{NH}_2$, $-\text{NMe}_2$, $-\text{OH}$, $-\text{OMe}$, $-\text{NHSO}_2\text{Me}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(=\text{O})-\text{OMe}$, $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{CH}_3$, $-\text{NHC}(=\text{O})\text{Me}$, $-\text{C}(=\text{O})\text{N}(-\text{Me})_2$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(-\text{Me})_2$, $-\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CO}_2\text{H}$, $-\text{OCH}_2\text{C}(=\text{O})-\text{OMe}$, $-\text{OCH}_2\text{C}(=\text{O})-\text{NH}_2$ and $-\text{OCH}_2\text{C}(=\text{O})\text{N}(-\text{Me})_2$.

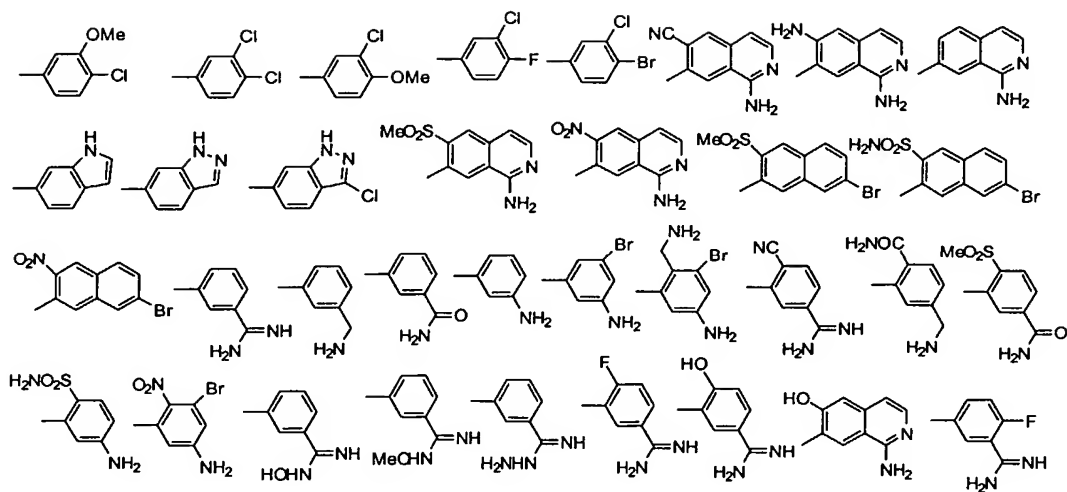
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J is a member selected from the group consisting of:
a direct link, -O-, -NH-, -C(=O)-NH- and -NH-C(=O)-;

5 X is a member selected from the group consisting of:

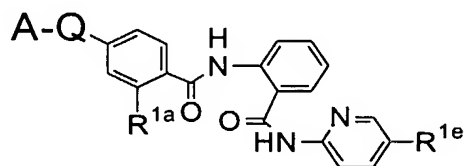




and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

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4. A compound of claim 1, having the following structure:



wherein:

R^{1a} is a member selected from the group consisting of:

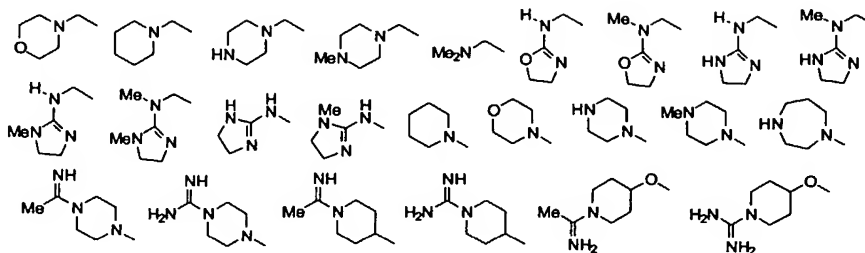
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H, -F, -Cl and -Br;

R^{1e} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, -OH, -Me, -CF₃ and -CH₂NH₂; and

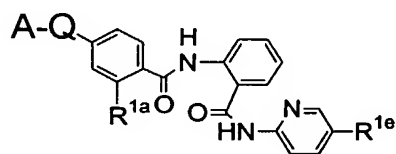
A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

5

6. A compound of claim 1 having the following structure:



wherein:

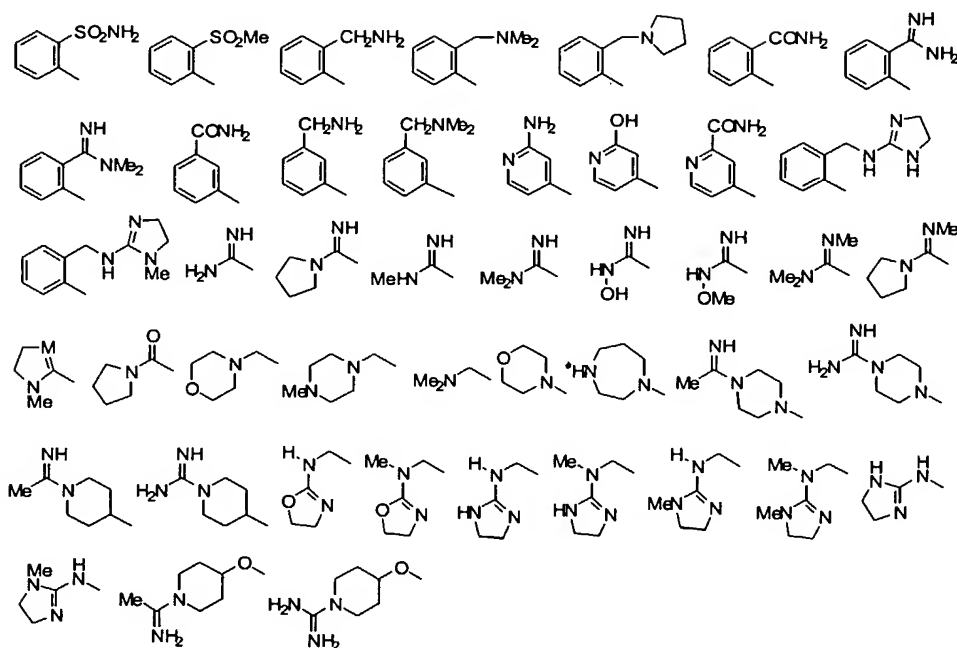
10 R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and -Br;

R^{1e} is a member selected from the group consisting of:

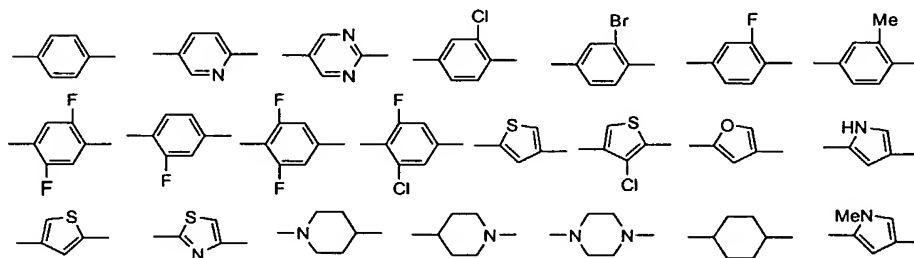
H, -F, -Cl, -Br, -OMe, -OH, -Me, -CF₃ and -CH₂NH₂;

A-Q is a member selected from the group consisting of:



D is a member selected from the group consisting of:

5



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

10 8. A compound of claim 1 having the following structure:

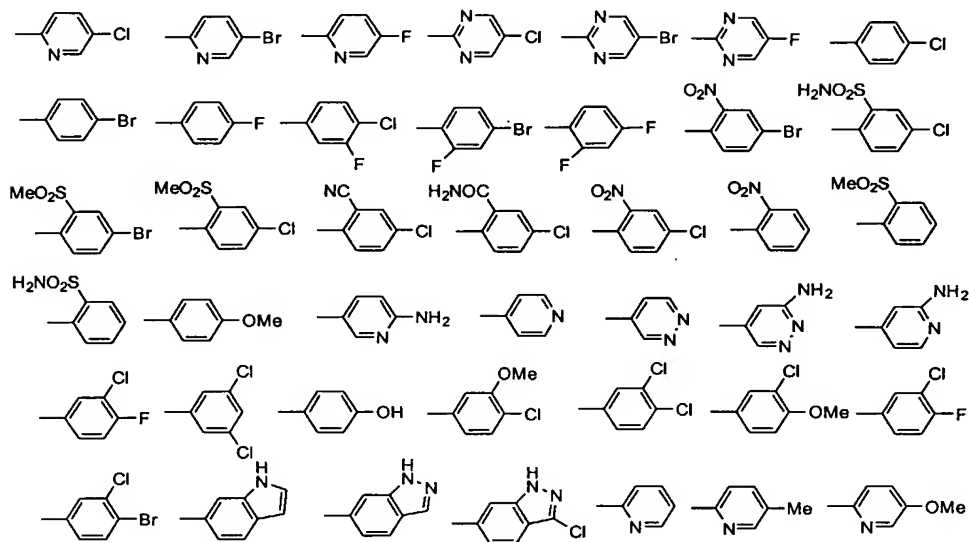


wherein:

J is a member selected from the group consisting of:

5 -NHC(=O)-, -C(=O)NH-;

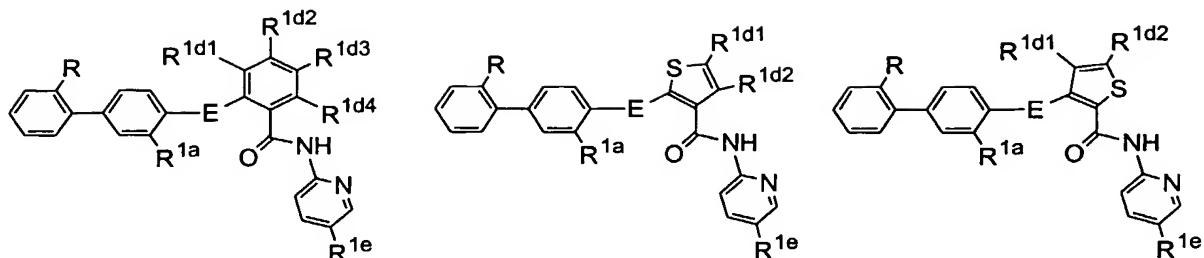
X is a member selected from the group consisting of:



10 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and
prodrug derivatives thereof.

9. A compound of claim 1 having the following structure:

191



wherein:

R is a member selected from the group of :

-SO₂-NH₂ and -SO₂Me;

5

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

E is a member selected from the group consisting of:

10

-NHC(=O)- and -C(=O)NH-;

R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

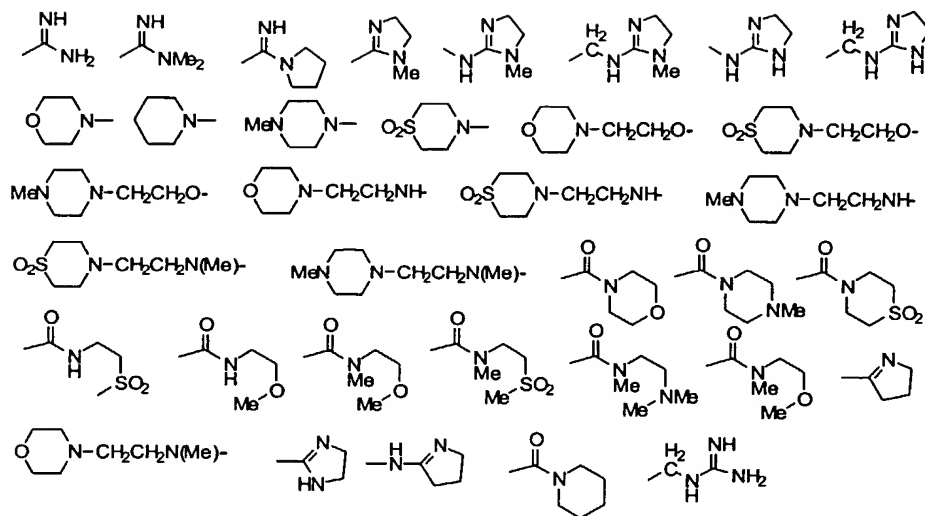
H, -F, -Cl, -Br, -Me, -NO₂, -OH, -OMe, -NH₂, -NHAc, -NHSO₂Me, -CH₂OH
and -CH₂NH₂;

15

R^{1d3} is a member selected from the group of:

H, -CH₃, -CF₃, -Cl, -F, -Br, -NH₂, -N(-Me)₂, -OH, -OMe, -NHSO₂Me, -NO₂,
-CN, -C(=O)-OMe, -CO₂H, -C(=O)-NH₂, -SO₂NH₂, -SO₂CH₃, -NHC(=O)-Me,
-C(=O)-N(-Me)₂, -CH₂NH₂, -CH₂-N(-Me)₂, -CH₂OH, -OCH₂CO₂H,
-OCH₂C(=O)-OMe, -OCH₂C(=O)-NH₂, and -OCH₂C(=O)-N(-Me)₂,

20

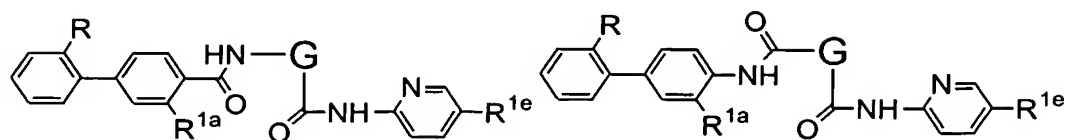


R^{1c} is a member selected from the group of :

F, -Cl, -Br, -OH, -Me and -Ome,

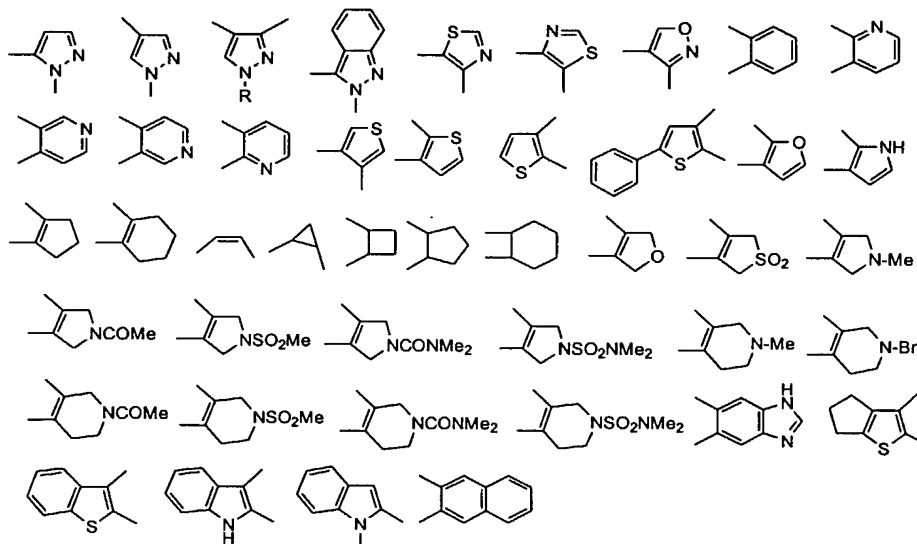
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

10. A compound of claim 1 having the following structure:



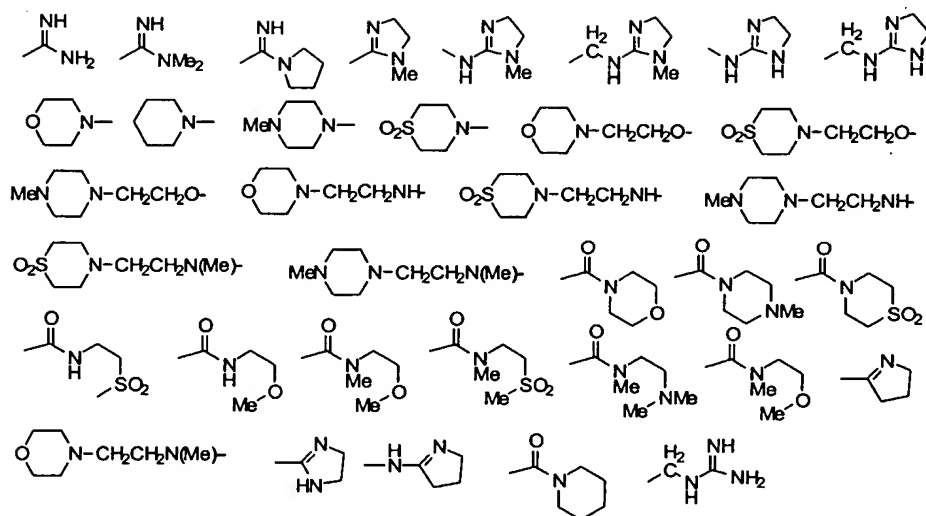
wherein:

- 5 R is a member selected from the group consisting of:
-SO₂NH₂, -SO₂Me;
R^{1a} is a member selected from the group consisting of:
H, -F, -Cl and Br;
R^{1c} is a member selected from the group consisting of:
10 H, -F, -Cl, -Br, -OMe, -OH, -Me, -CF₃ and -CH₂NH₂; and
G is a member selected from the group consisting of:



wherein each G group may be substituted by 0-4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

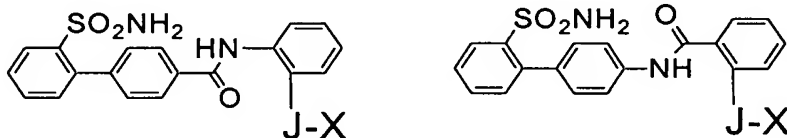
- 15 H, -CH₃, -CF₃, -Cl, -F, -Br, -NH₂, -N(-Me)₂, -OH, -OMe, -NHSO₂Me, -NO₂,
-CN, -C(=O)-OMe, -CO₂H, -C(=O)-NH₂, -SO₂NH₂, -SO₂CH₃, -NH-C(=O)-Me,
-C(=O)-N(-Me)₂, -CH₂NH₂, -CH₂-N(-Me)₂, -CH₂OH, -OCH₂CO₂H,
-OCH₂CO₂Me, -OCH₂C(=O)-NH₂, -OCH₂C(=O)-N(-Me)₂



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

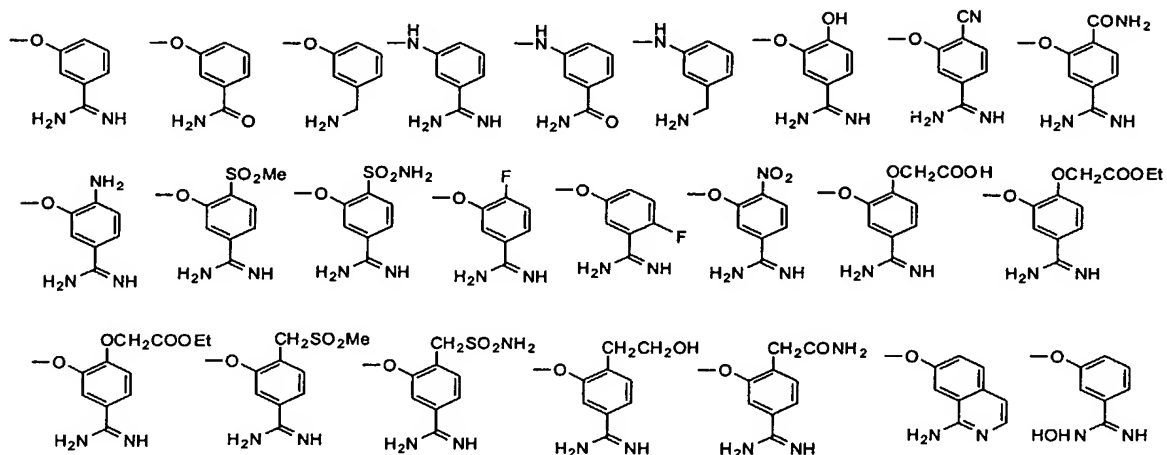
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11. A compound of claim 1 having the following structure:



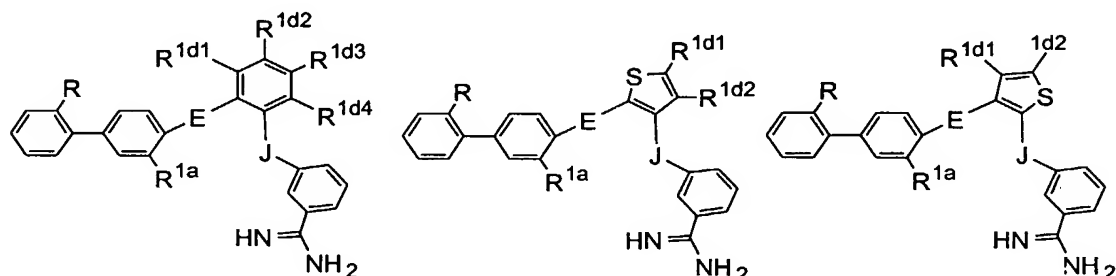
10 wherein:

J-X are collectively a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and
5 prodrug derivatives thereof.

12. A compound of claim 1 having the following structure:



wherein:

R is a member selected from the group of :

10 $-\text{SO}_2\text{NH}_2$, and $-\text{SO}_2\text{Me}$;

R^{1a} is a member selected from the group of:

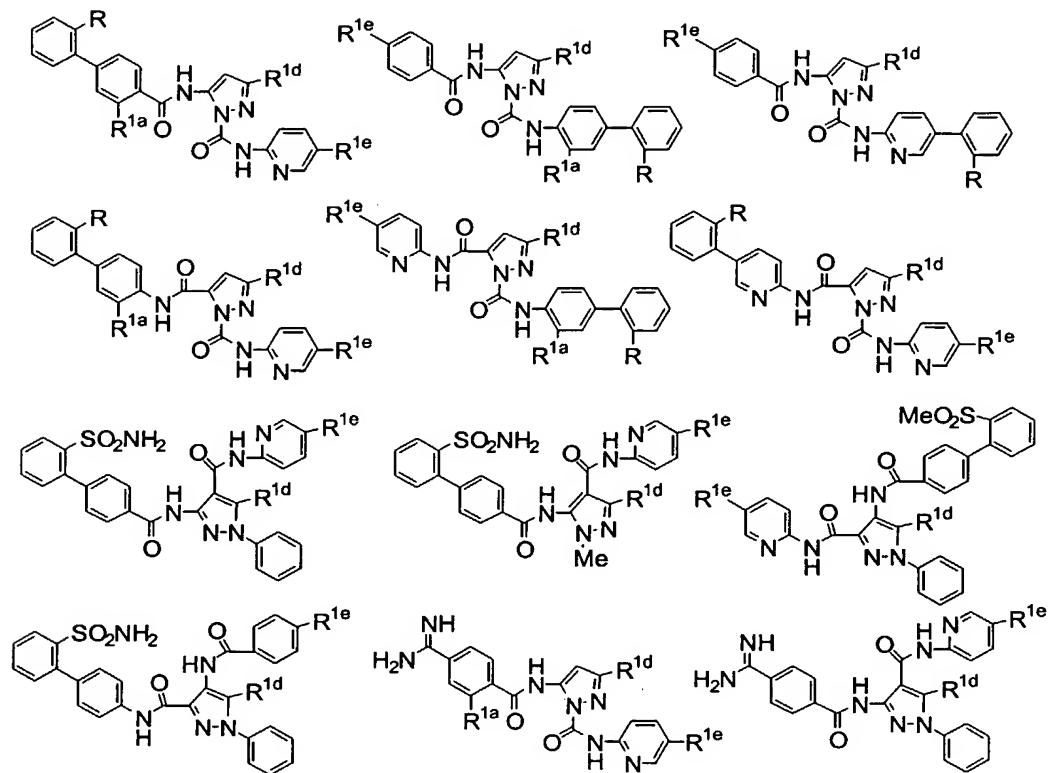
H, -F, -Cl and Br;

15 E is a member selected from the group consisting of:

-NHC(=O)- and -C(=O)NH-;

J is a member selected from the group consisting of:

13. A compound of claim 1 selected from the group consisting of:



5

wherein:

R is a member selected from the group of:

-SO₂-NH₂, and -SO₂Me;

10

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

R^{1d} is a member selected from the group consisting of:

-H, -CH₃, -CF₃, -CN, -SO₂NH₂ and -SO₂CH₃; and

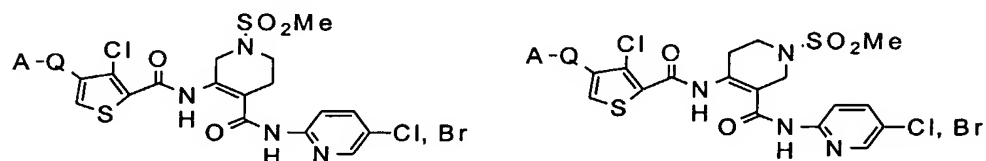
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R^{1e} is a member selected from the group of:

-Cl and -Br;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

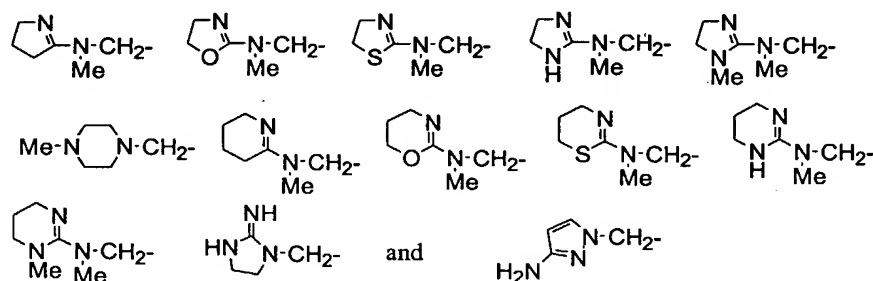
- 5 14. A compound of claim 1 having the following structure:



wherein:

10

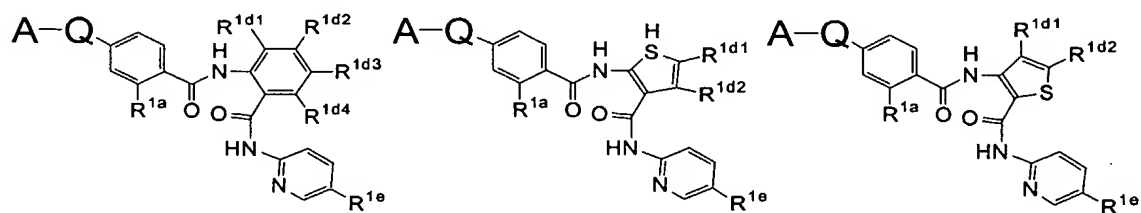
A-Q taken together are a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and

- 15 prodrug derivatives thereof.

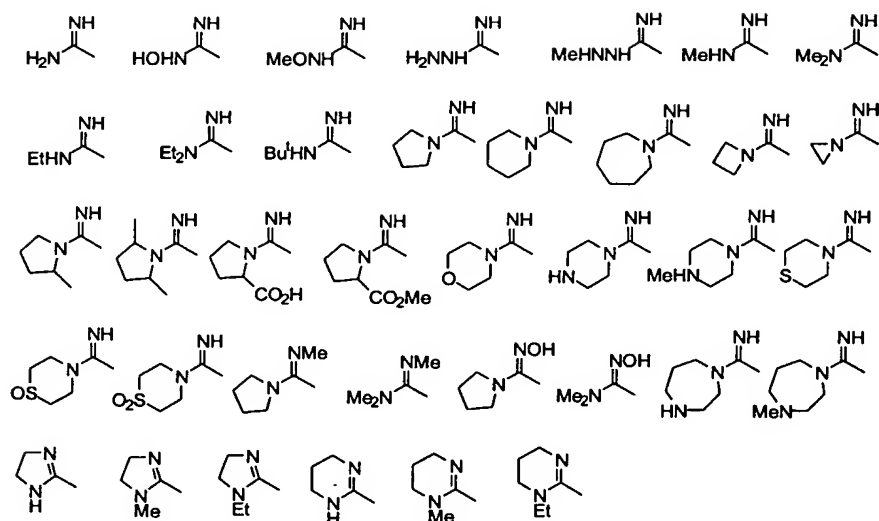
15. A compound of claim 1 selected from the group consisting of:



wherein:

A-Q is a member selected from the group of :

5



R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

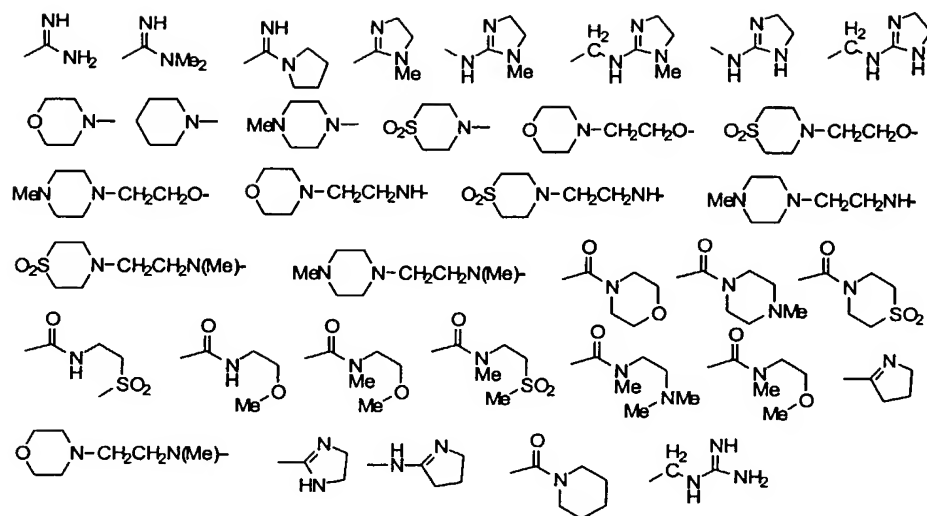
10

R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

H, -F, -Cl, -Br, -Me, -NO₂, -OH, -OMe, -NH₂, -NHAc, -NHSO₂Me, -CH₂OH, -CH₂NH₂

15 R^{1d3} is a member selected from the group of:

H, -CH₃, -CF₃, -Cl, -F, -Br, -NH₂, -N(-Me)₂, -OH, -OMe, -NHSO₂Me, -NO₂, -CN, -C(=O)-OMe, -CO₂H, -C(=O)-NH₂, -SO₂NH₂, -SO₂CH₃, -NHC(=O)-Me, -C(=O)-N(Me)₂, -CH₂NH₂, -CH₂-N(-Me)₂, -CH₂OH, -OCH₂CO₂H, -OCH₂C(=O)-OMe, -OCH₂C(=O)-NH₂, -OCH₂C(=O)-N(-Me)₂.



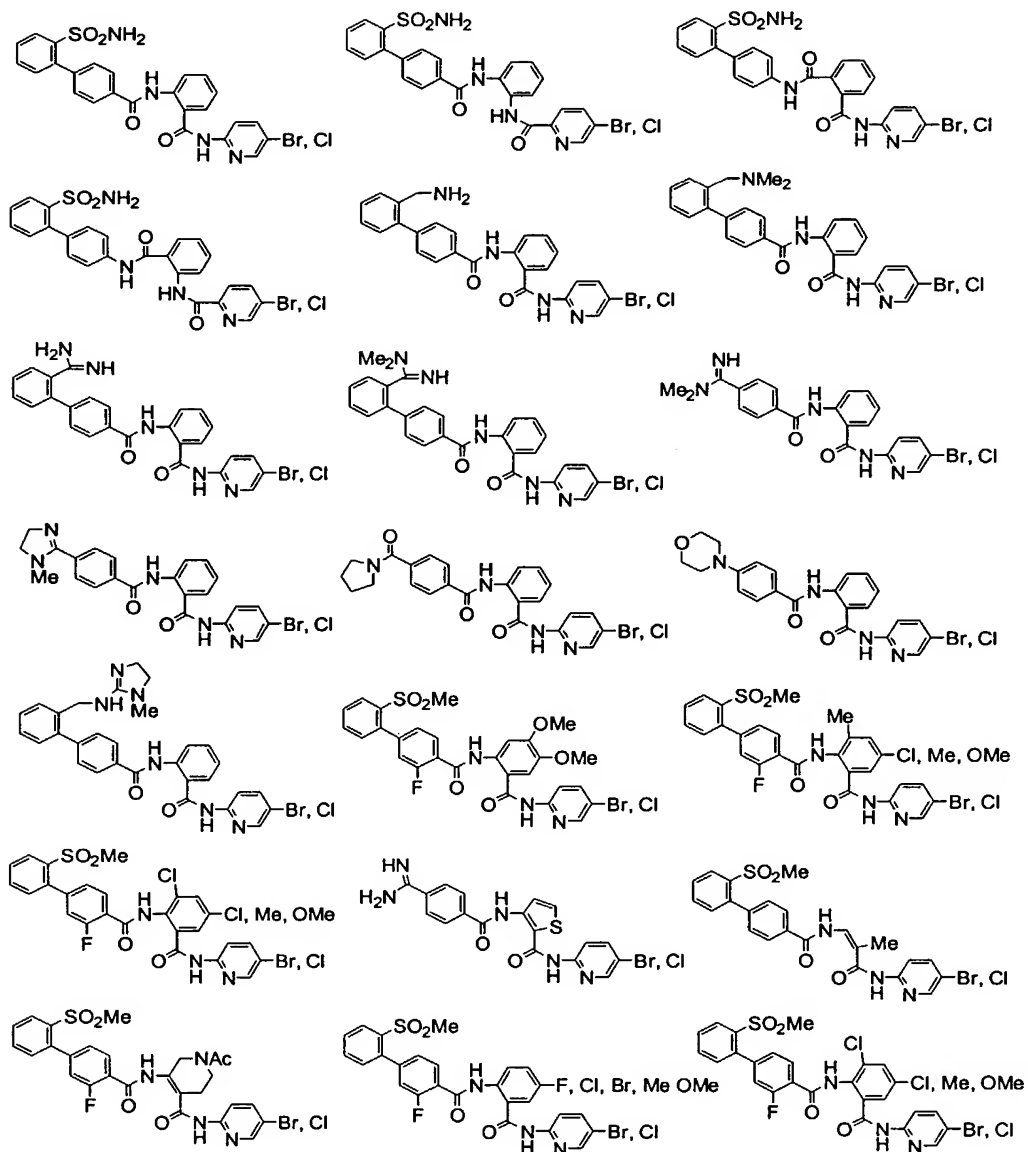
R^{1e} is a member selected from the group of:

F, -Cl, -Br, -OH, -Me and -OMe;

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and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

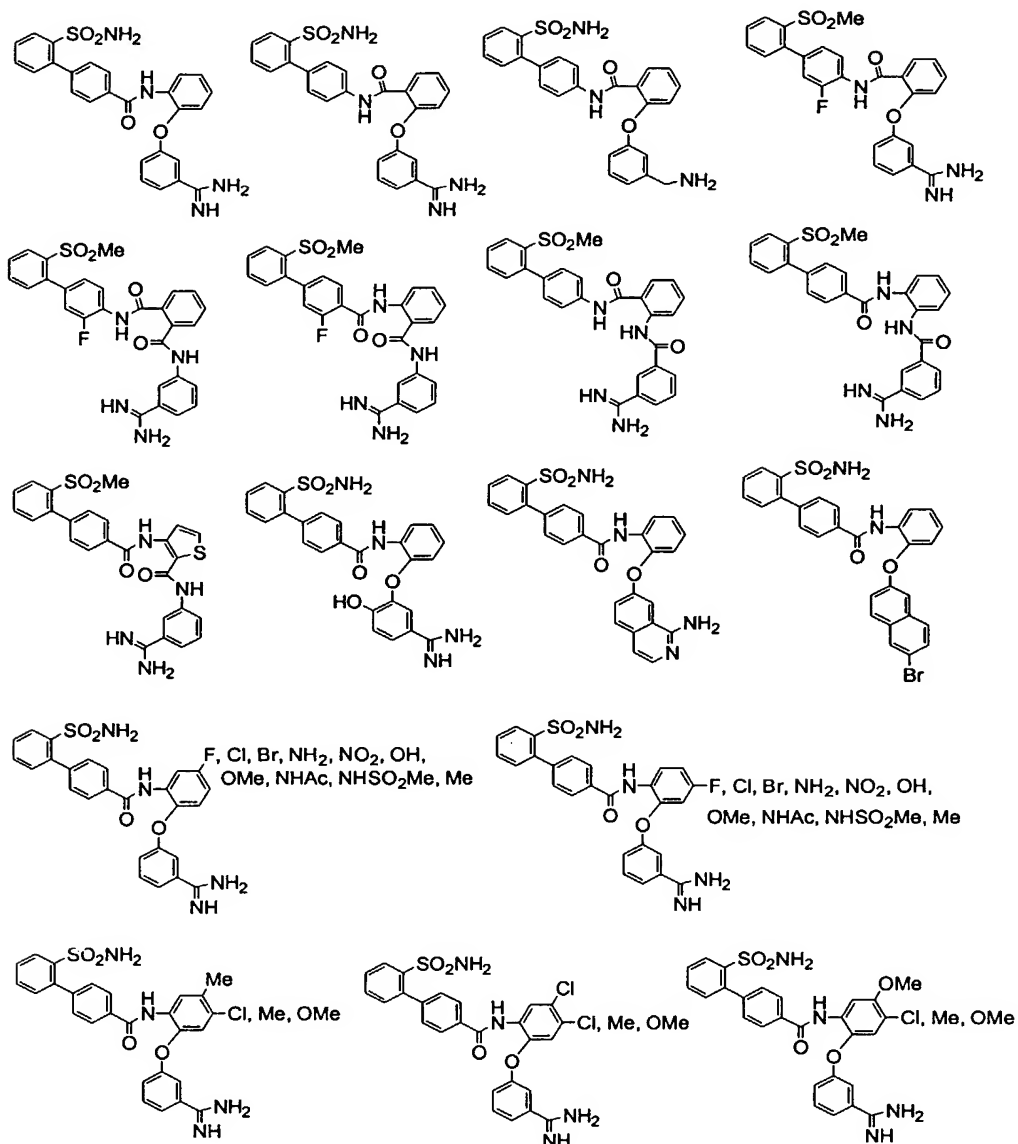
16. A compound of claim 1 selected from the group of consisting of:



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and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

17. A compound of claim 1 selected from the group consisting of:



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and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

18. A compound of claim 1 selected from the group consisting of:

- 3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzamidine, 3-(4-fluoro-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine, 3-(4-trifluoromethyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy)
- 5 benzamidine, 3-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine, 3-(5-hydroxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine, 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine, 3-(4-hydroxycarbonyl-2-(4-[(2-
- 10 aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine, 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pheylamino) benzamidine, 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)phenoxy)-1-aminoisoquinoline, 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy)1-aminoisoquinoline, 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy)1-
- 15 aminoisoquinoline, 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy)1-aminoisoquinoline, 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine, 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzamidine, 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy)
- 20 benzamidine, 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-bromophenoxy) benzamidine, 2-bromo-6-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene, 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene, 3-hydroxycarbonyl-2-(4-[(2-
- 25 aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene, 3-aminocarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene, 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene, 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene, N-(5-bromo-2-pyridinyl)-(2-(4-[(2-
- 30 aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide, N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide,

- N-(5-chloro-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide, N-(4-bromo-2-methoxycarbonylphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide, N-(4-chloro-2-methoxycarbonylphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)pyridinyl-3-carboxamide,
- 5 N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)pyridinyl-3-carboxamide, N-(5-bromo-2-pyridinyl)-(3-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)pyridinyl-2-carboxamide, N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)pyridinyl-3-carboxamide, N-(4-bromo-2-nitrophenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide, N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide, N¹-(5-bromopyridin-2-yl)-N⁴-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide, N¹-(5-bromopyridin-2-yl)-N⁴-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide, N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide, N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide, N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide, N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazolyl)phenylcarbonyl)amino)-phenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-(4-[1,1-doxo(1,4-thiazaperhydroin-4-yl)]iminimethyl)phenylcarbonyl)amino)-phenylcarboxamide, N-(5-bromo-2-
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- 15
- 20
- 25
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- 35

- pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl))iminomethyl]phenylcarbonyl)amino)-phenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)-4,5-difluorophenylcarboxamide, 3-(2-(4-[(2-aminosulfonyl)phenyl]-2-fluorophenylaminocarbonyl-4-aminophenoxy) benzamidine, 3-(2-(4-[(2-aminosulfonyl)phenyl]-2-fluorophenylaminocarbonyl-4-aminophenoxy) benzamidine, 3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzylamine, 2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]-benzenecarboxamidine, (4-{2-[(dimethylamino)iminomethyl]phenyl}phenyl)-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl} {4-[2-((hydroxyamino)iminomethyl)-phenyl]phenyl}carboxamide, 2-[4-(N-{2-[N-(5-chloro(2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]benzamide, {4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide, [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl} {4-[(2-imidazolin-2-ylamino)methyl]phenyl}carboxamide, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl} {4-[(1-methyl(2-imidazolin-2-yl))amino]methyl}phenyl}carboxamide, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)} {4-(1-methyl(2-imidazolin-2-yl))phenyl}carboxamide, {4-[(dimethylamino)iminomethyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carboxamide, 4-(N-{2-[N-(5-chloro(2-pyridyl)carbamoyl]-3-thienyl}carbamoyl)benzenecarboxamidine, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)} {4-(iminopiperidylmethyl)-phenyl}carboxamide, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)} {4-(iminopyrrolidinylmethyl)-phenyl}carboxamide, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)} {4-(iminomorpholin-4-ylmethyl)phenyl}carboxamide, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)} {4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl}carboxamide, [4-(azaperhydroepinyliminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carboxamide, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)} {4-[imino(2-methylpyrrolidinyl)methyl]phenyl}carboxamide, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)} {4-[imino(methylamino)methyl]phenyl}carboxamide, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)} {4-(3-methyl(3,4,5,6-tetrahydropyrimidin-2-yl))phenyl}carboxamide, N-{2-[N-(5-chloro(2-

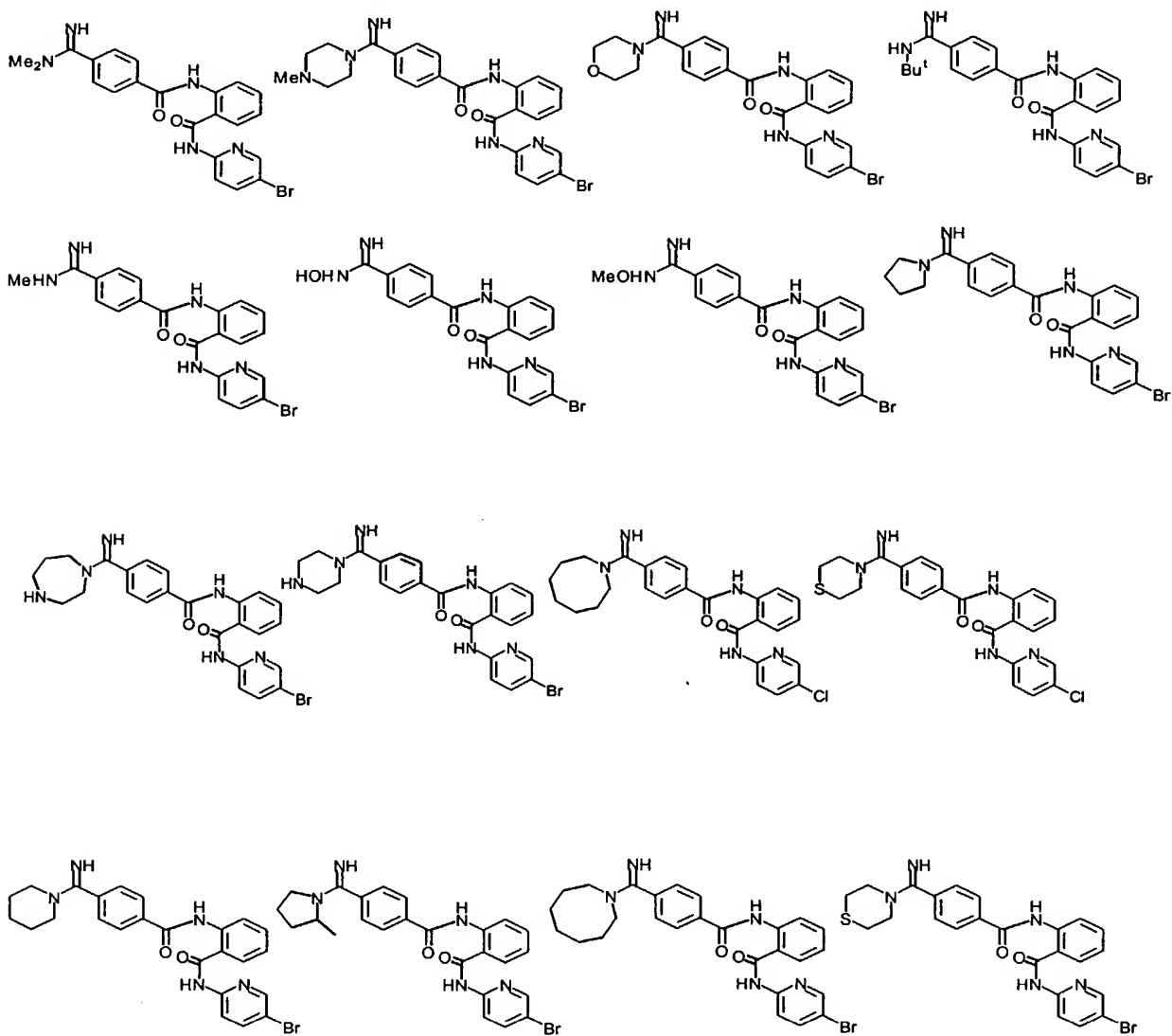
- pyridyl))carbamoyl](3-thienyl))[4-((hydroxyamino)iminomethyl)-phenyl]carboxamide, 1- {[4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl))carbamoyl}phenyl]-iminomethyl}pyrrolidine-2-carboxylic acid, N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl))[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide, 4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-3-thienyl}carbamoyl)benzenecarboxamidine, N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl))[4-(iminopyrrolidinylmethyl)phenyl]carboxamide, N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl))[4-(iminopiperidylmethyl)phenyl]carboxamide, N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl))[4-(iminomorpholin-4-ylmethyl)phenyl]carboxamide, N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl))[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carboxamide, N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl))[4-(iminopyrrolidinylmethyl)phenyl]carboxamide, N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl))[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide, 3-[(3-{[4-(2-sulfamoylphenyl)phenyl]carbonylamino}-2-thienyl)carbonylamino]benzenecarboxamidine, N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl))[4-(2-sulfamoylphenyl)phenyl]carboxamide, N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl))[4-(2-sulfamoylphenyl)phenyl]carboxamide, N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl)5-methyl-pyrazolcarboxamide, N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)-5-fluorophenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonylamino)-5-fluorophenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenylcarboxamide, N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide, N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4,5-dimethoxyphenyl}(4-cyanophenyl)carboxamide, (4,5-dimethoxy-2-{[4-(1-methyl(2-imidazolin-2-yl))phenyl]carbonylamino}phenyl)-N-(5-bromo(2-pyridyl))carboxamide, 4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4,5-dimethoxyphenyl}carbamoyl)-benzenecarboxamidine, N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}-carboxamide, N-(5-chloro(2-pyridyl))(5-methoxy-2-{[4-(1-methyl(2-imidazolin-2-yl))phenyl]carbonylamino}phenyl)carboxamide, 4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methoxyphenyl}carbamoyl)benzene-carboxamidine, N-(5-chloro(2-pyridyl))[2-({4-imino(methylamino)methyl}phenyl)carbonylamino]-5-methoxyphenyl]carboxamide,

- [2-({4-[(dimethylamino)iminomethyl]phenyl} carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, N-(5-chloro(2-pyridyl))(2-{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide, N-(5-chloro(2-pyridyl))(2-{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide, N-(5-chloro(2-pyridyl))(2-{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide, N-(5-chloro(2-pyridyl))(2-{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide, (2-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide, N-(5-bromo(2-pyridyl))(2-{[4-(cyanophenyl)carbonylamino]-5-methoxyphenyl} carboxamide, N-(5-bromo(2-pyridyl))(5-methoxy-2-{[4-(1-methyl(2-imidazolin-2-yl))phenyl]carbonylamino} phenyl)carboxamide, 4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4-methoxyphenyl} carbamoyl)benzenecarboxamidine, N-(5-bromo(2-pyridyl))[2-({4-[imino(methylamino)methyl]phenyl} carbonylamino)-5-methoxyphenyl]carboxamide, [2-({4-[(dimethylamino)iminomethyl]phenyl} carbonylamino)-5-methoxyphenyl]-N-(5-bromo(2-pyridyl))carboxamide, N-(5-chloro(2-pyridyl))(2-{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide, N-(5-bromo(2-pyridyl))(2-{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide, N-(5-bromo(2-pyridyl))(2-{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide, N-(5-bromo(2-pyridyl))(2-{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide, (2-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide, N-(5-chloro(2-pyridyl)){6-[4-(cyanophenyl)carbonylamino]-3-hydroxyphenyl} carboxamide, ethyl 2-{3-[N-(5-chloro(2-pyridyl))carbamoyl]-4-[(4-cyanophenyl)carbonylamino]-phenoxy} acetate, methyl 2-[4-({4-[(dimethylamino)iminomethyl]phenyl} carbonylamino)-3-[N-(5-chloro(2-pyridyl))carbamoyl]phenoxy} acetate, (6-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-3-hydroxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide, 4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-hydroxyphenyl} carbamoyl)-benzenecarboxamidine, and 4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-hydroxyphenyl} carbamoyl)-benzenecarboxamidine,

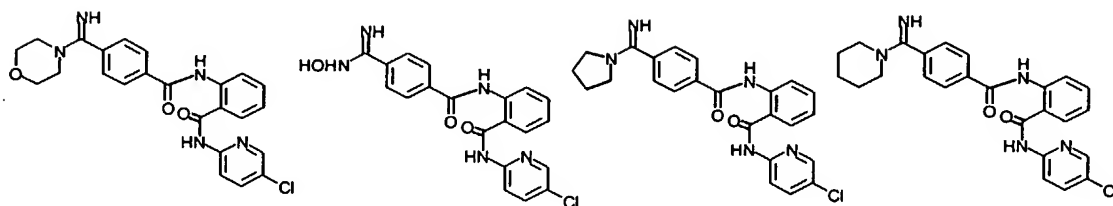
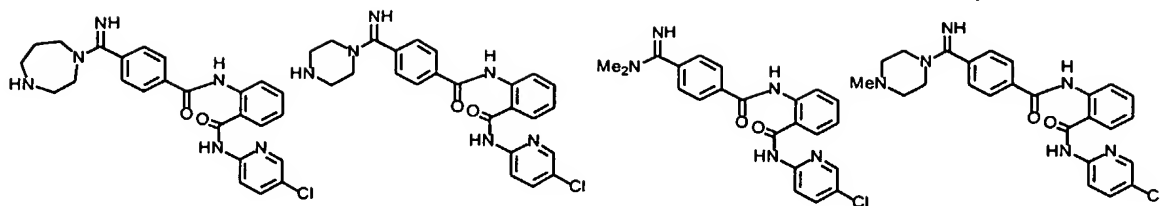
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

19. The compound according to claim 1 selected from the group consisting of:

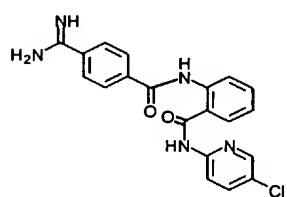
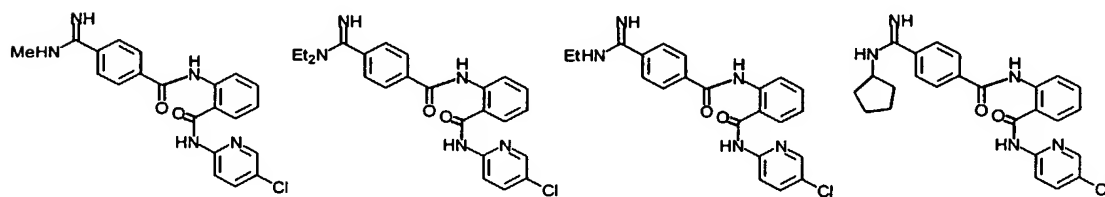
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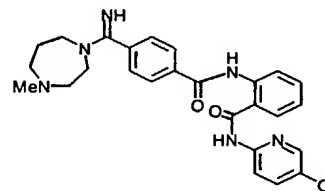
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and

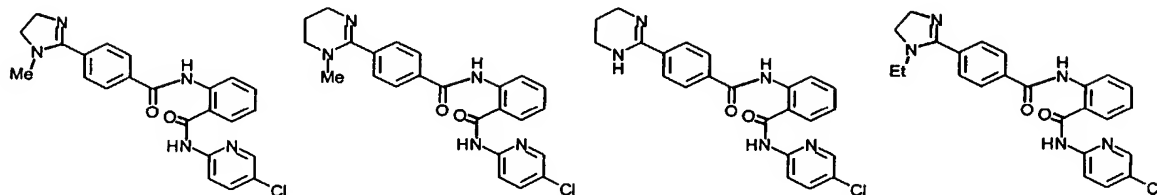


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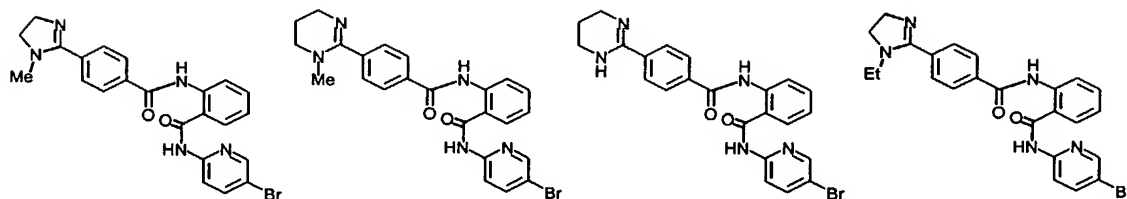
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

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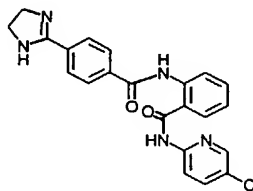
20. The compound according to claim 1 selected from the group consisting of:



5



and



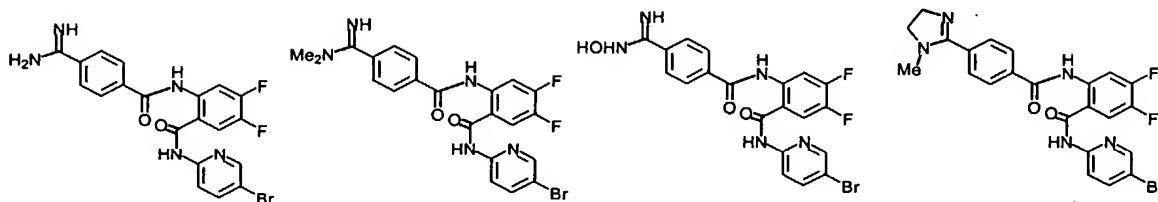
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and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

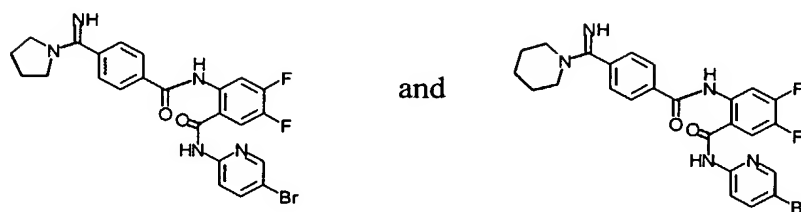
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21. The compound according to claim 1 selected from the group consisting of:



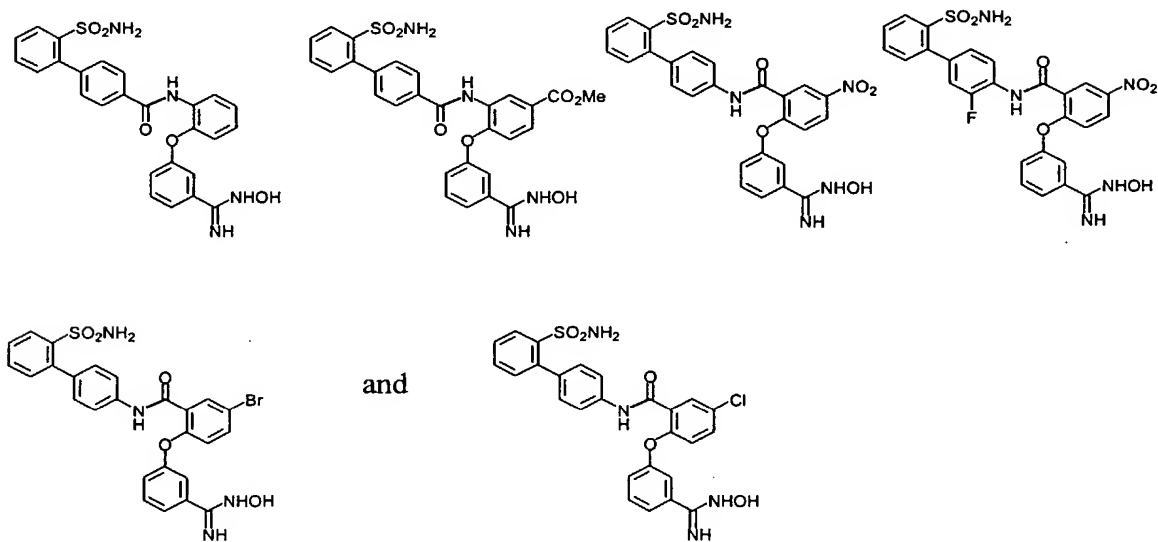
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and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

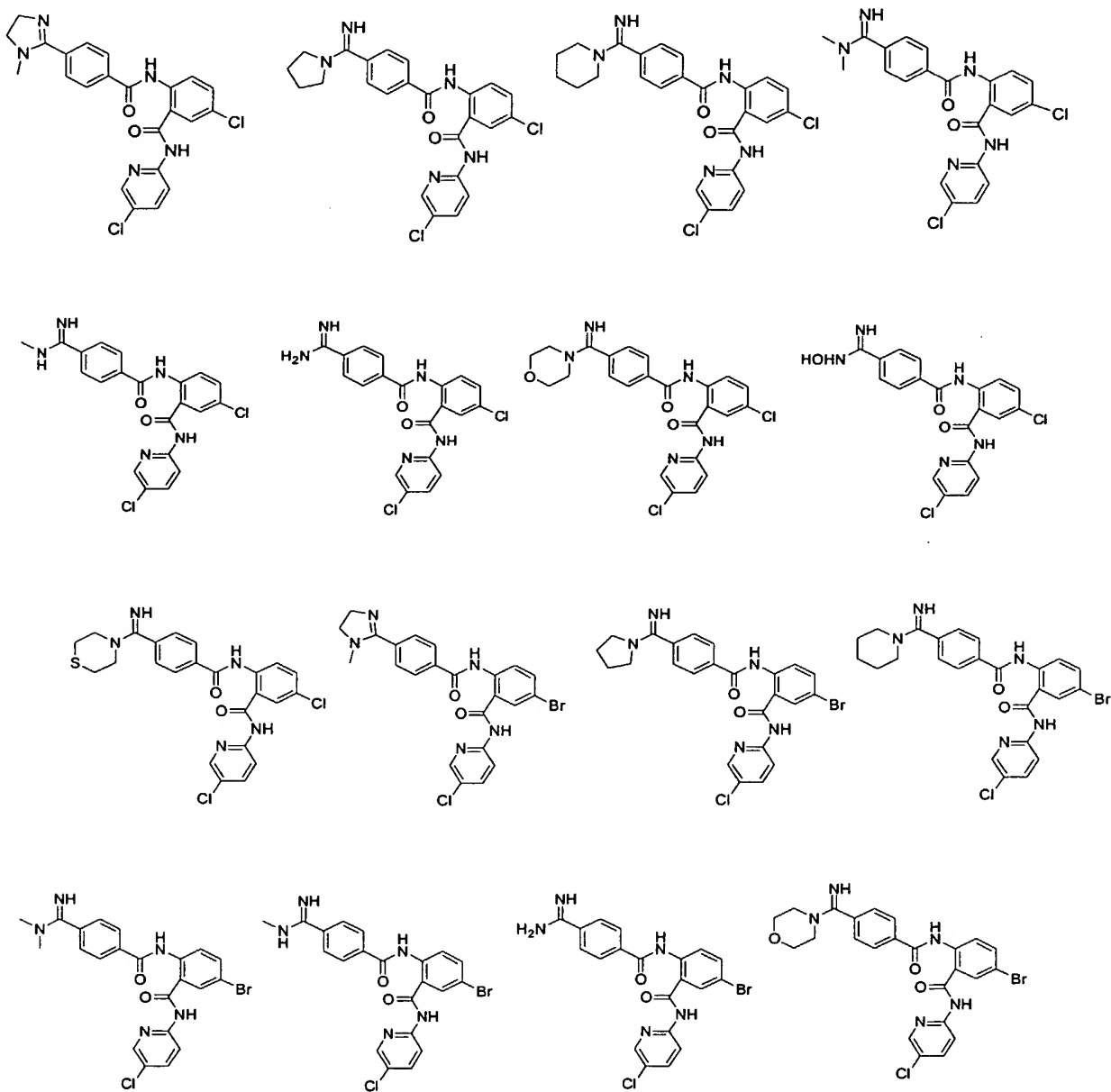
22. The compound according to claim 1 selected from the group consisting of:

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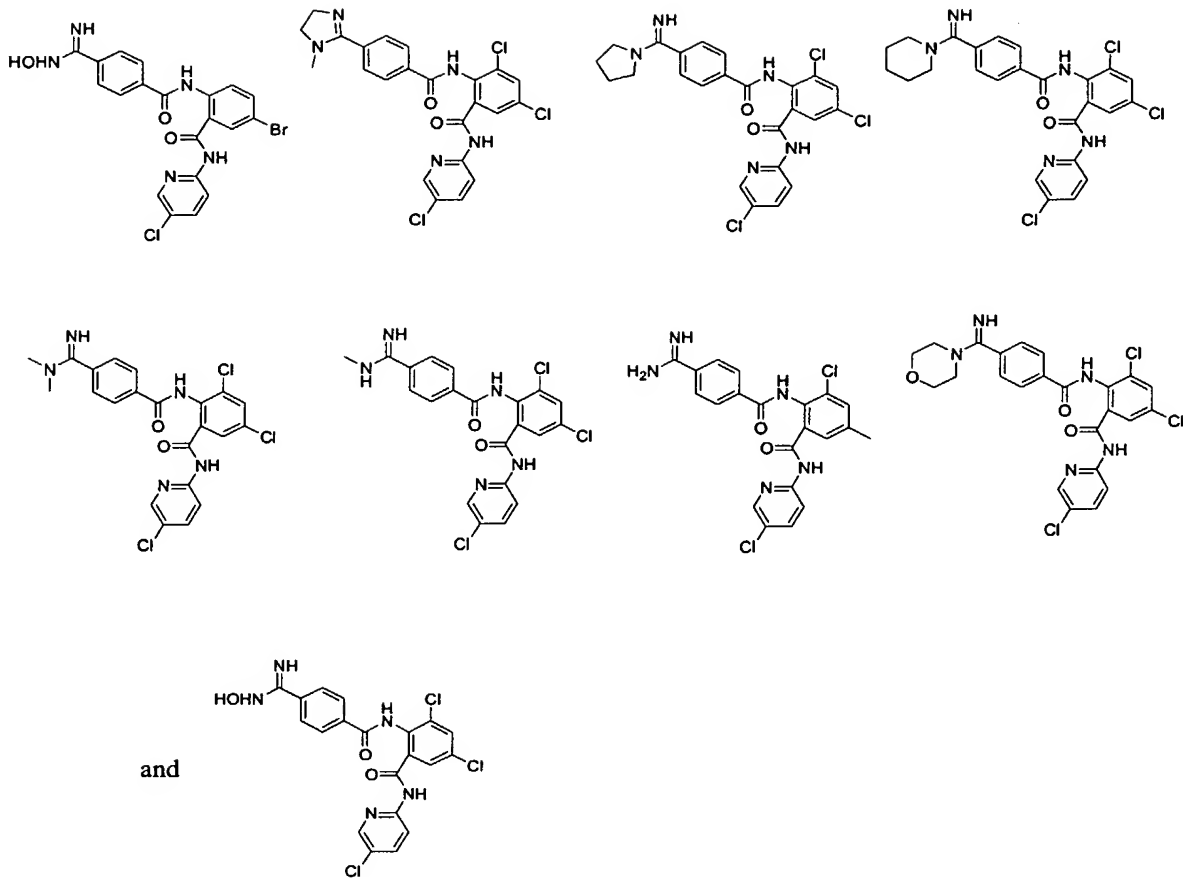


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

23. The compound according to claim 1 selected from the group consisting of:



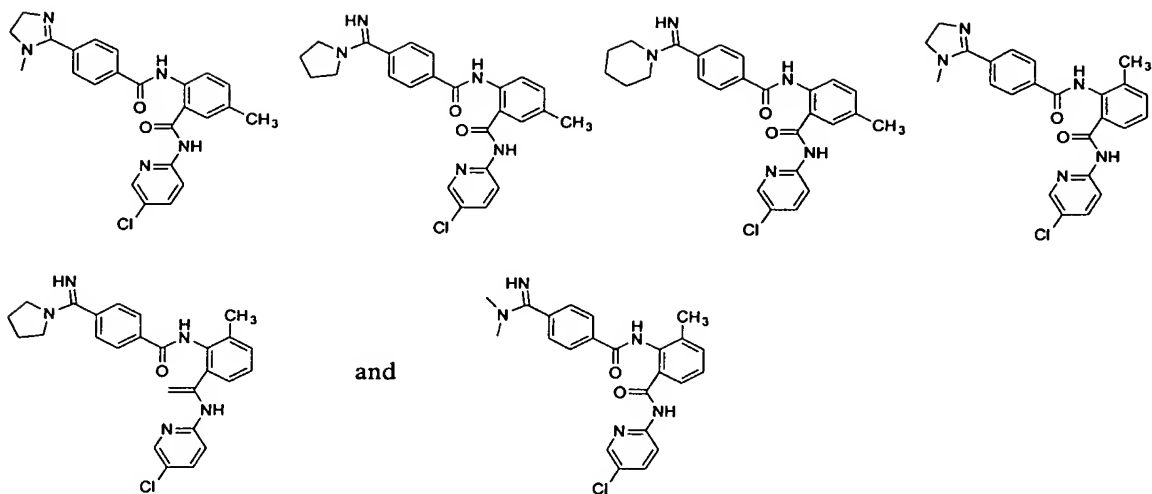
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- 5 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

24. The compound according to claim 1 selected from the group consisting of:

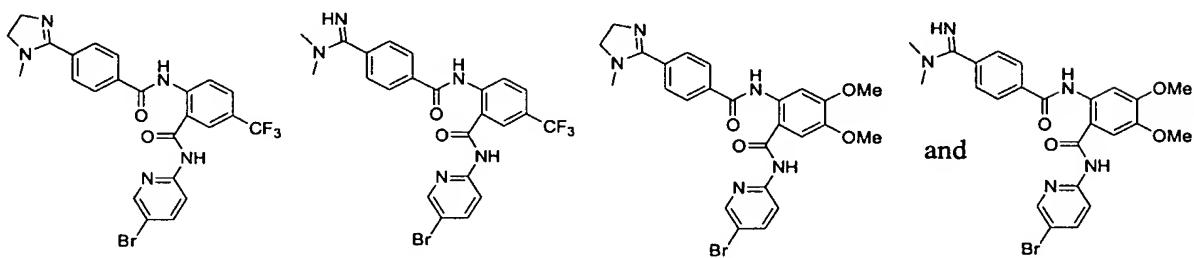
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and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

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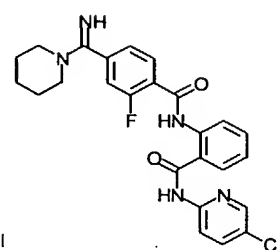
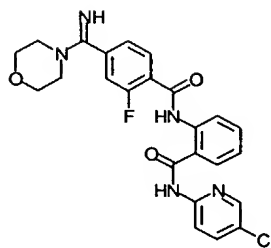
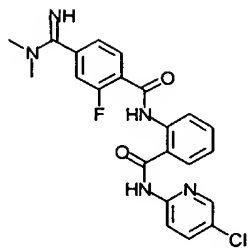
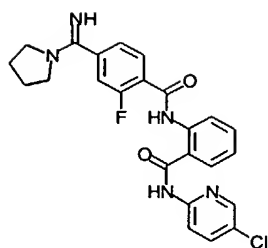
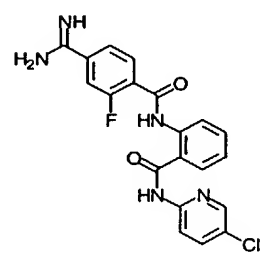
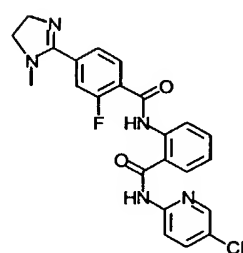
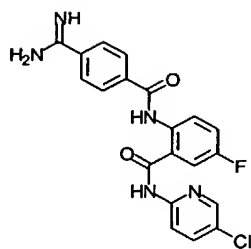
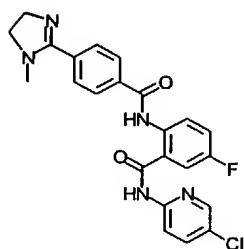
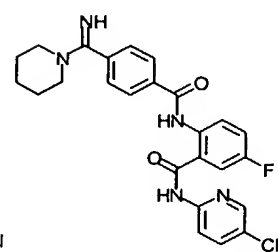
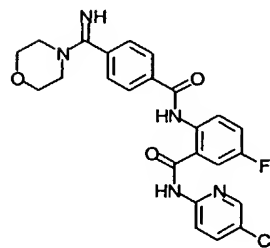
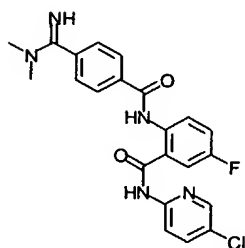
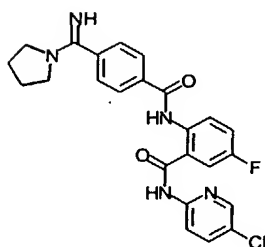
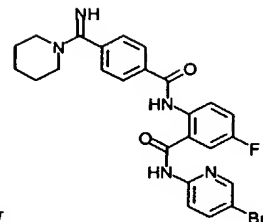
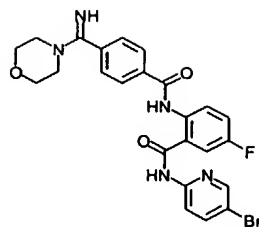
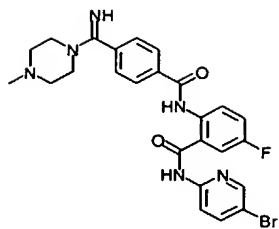
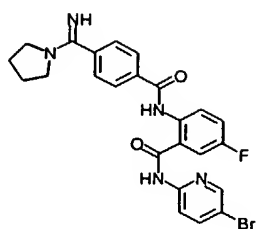
25. The compound according to claim 1 selected from the group consisting of:

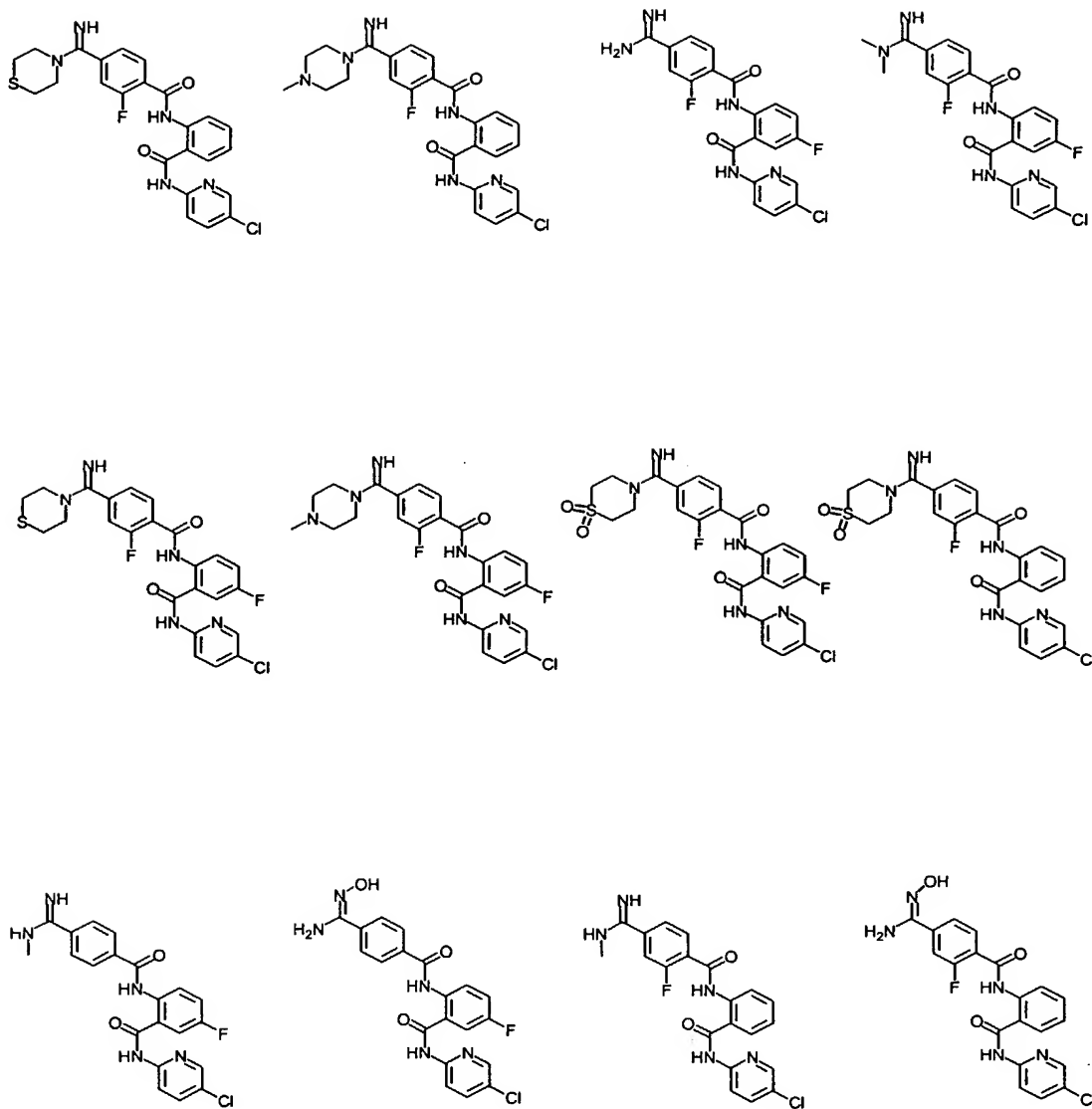


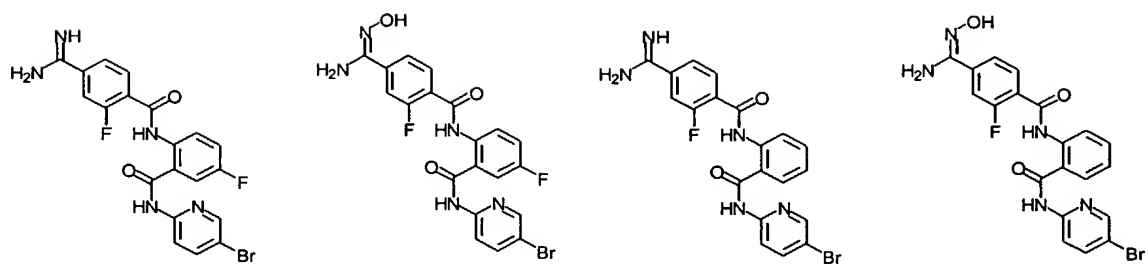
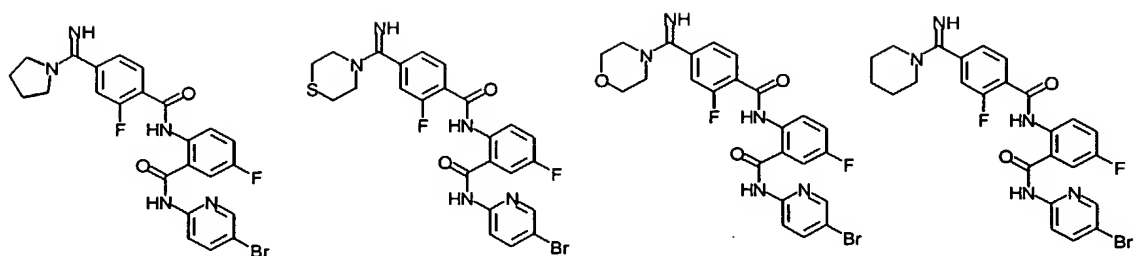
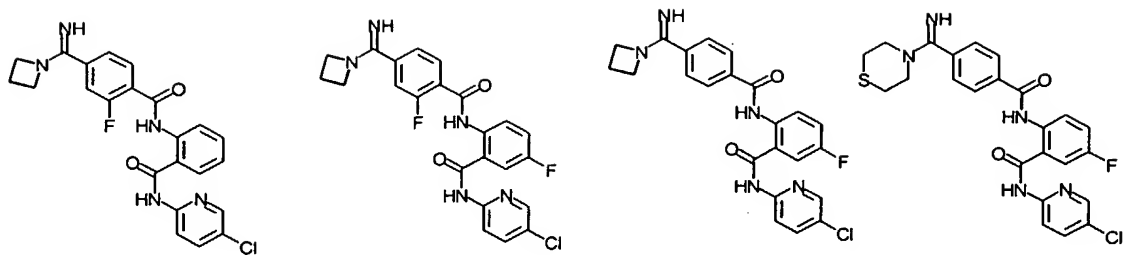
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

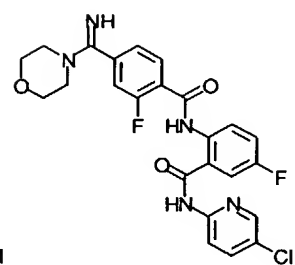
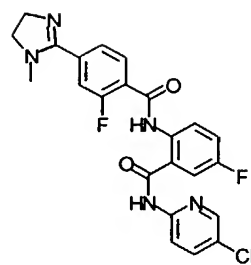
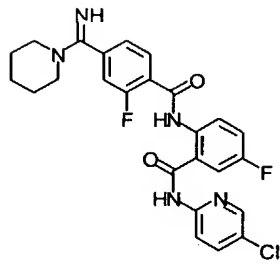
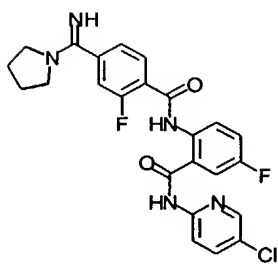
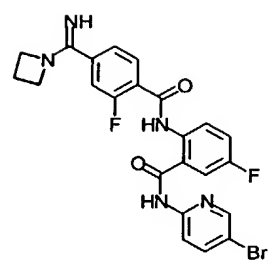
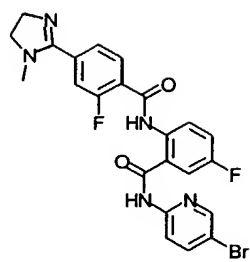
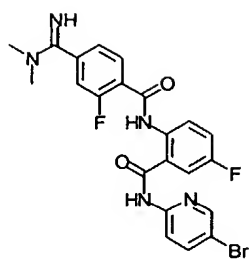
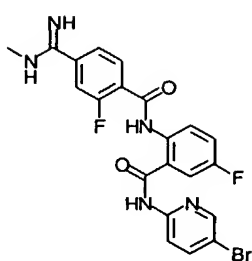
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26. The compound according to claim 1, which is a member selected from the group consisting of:

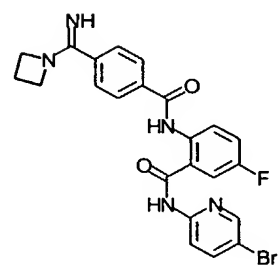
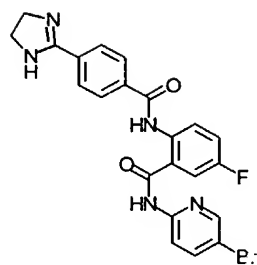
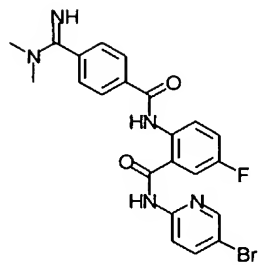
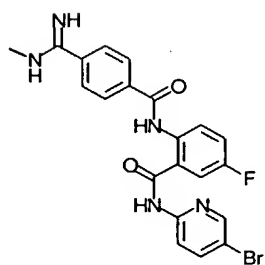




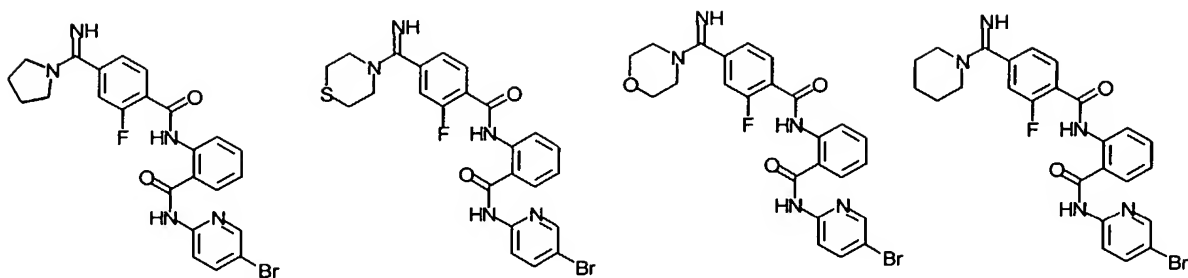




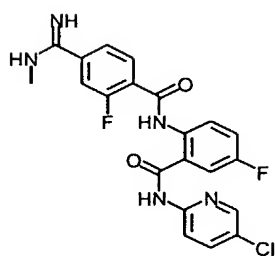
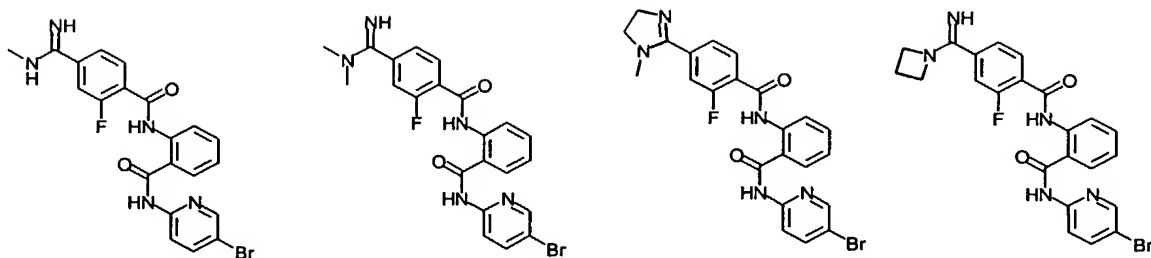
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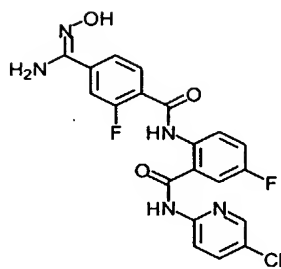
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5



and



10 and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

27. A pharmaceutical composition for preventing or treating a condition in a

28. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of a compound of claim 1.

29. The method of claim 28, wherein the condition is selected from the group
5 consisting of:

acute coronary syndrome, myocardial infarction, unstable angina, refractory
angina, occlusive coronary thrombus occurring post-thrombolytic therapy or
post-coronary angioplasty, a thrombotically mediated cerebrovascular
syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks,
10 venous thrombosis, deep venous thrombosis, pulmonary embolus,
coagulopathy, disseminated intravascular coagulation, thrombotic
thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease
associated with heparin-induced thrombocytopenia, thrombotic complications
associated with extracorporeal circulation, thrombotic complications
15 associated with instrumentation, and thrombotic complications associated with
the fitting of prosthetic devices.

30. A method for inhibiting the coagulation of biological samples, comprising the
step of administering a compound of claim 1.

20

31. A pharmaceutical composition for preventing or treating a condition in a
mammal characterized by undesired thrombosis comprising a pharmaceutically
acceptable carrier and a pharmaceutically effective amount of a compound of claim 2.

25 32. A method for preventing or treating a condition in a mammal characterized by
undesired thrombosis comprising administering to said mammal a therapeutically
effective amount of a compound of claim 2.

33. The method of claim 32, wherein the condition is selected from the group consisting of:

5 acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease
10 associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation, and thrombotic complications associated with the fitting of prosthetic devices.

15 34. A method for inhibiting the coagulation of biological samples, comprising the step of administering a compound of claim 2.

20 35. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of claim 3.

25 36. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of a compound of claim 3.

37. The method of claim 36, wherein the condition is selected from the group

post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation, and thrombotic complications associated with the fitting of prosthetic devices.

10

38. A method for inhibiting the coagulation of biological samples, comprising the step of administering a compound of claim 3.

15

39. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of claim 4.

20

40. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of a compound of claim 4.

41. The method of claim 40, wherein the condition is selected from the group consisting of:

25

acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular

5 thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease
associated with heparin-induced thrombocytopenia, thrombotic complications
associated with extracorporeal circulation, thrombotic complications
associated with instrumentation, and thrombotic complications associated with
the fitting of prosthetic devices.

42. A method for inhibiting the coagulation of biological samples, comprising the
step of administering a compound of claim 4.

(19) World Intellectual Property Organization
International Bureau



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217/22, 333/38, 401/12, 409/12, 409/14, 417/12, A61K
31/18, 31/33, A61P 7/02

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(21) International Application Number: PCT/US00/25196

(74) Agent: **LEE, Christine, S.**; Morgan, Lewis & Bockius LLP, 1800 M. Street, N.W., Washington, DC 20036-5869 (US).

(22) International Filing Date:
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(25) Filing Language: English

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Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BENZAMIDES AND RELATED INHIBITORS OF FACTOR Xa

(57) Abstract: Compounds of the formula A - Q - D - E - G - J - X in which D is a direct link, a substituted or unsubstituted phenyl or naphthyl group or a heterocyclic ring system; X is a substituted or unsubstituted phenyl or naphthyl group or a heterocyclic system; and the other variables are as defined in the claims, their salts and compositions related thereto having activity against mammalian factor Xa are disclosed. The compounds are useful in vitro or in vivo for preventing or treating coagulation disorders.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/25196

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C311/16 C07C311/46 C07C317/40 C07C317/44 C07D213/75
 C07D213/81 C07D213/82 C07D217/22 C07D333/38 C07D401/12
 C07D409/12 C07D409/14 C07D417/12 A61K31/18 A61K31/33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 57934 A (DU PONT MERCK PHARMACEUTICAL) 23 December 1998 (1998-12-23) page 2 -page 8; examples; table 1 ---	1-3, 27-42
X	WO 98 06694 A (DU PONT MERCK PHARMACEUTICAL) 19 February 1998 (1998-02-19) page 2 -page 7; examples; table 1A ---	1-3, 27-42
A	WO 98 28282 A (DU PONT MERCK PHARMACEUTICAL) 2 July 1998 (1998-07-02) page 3 -page 9; examples; table 1 ---	1-42
A	WO 98 28269 A (DU PONT MERCK PHARMACEUTICAL) 2 July 1998 (1998-07-02) page 3 -page 9; examples; table 1A --- -/--	1-42

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Date of the actual completion of the international search

26 February 2001

Date of mailing of the international search report

12/03/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/25196

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.D. YOUNG, ET AL.: "Interannular interactions in para-substituted diphenylmethane anion redicals" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 94, no. 25, 13 December 1972 (1972-12-13), pages 8790-8794, XP002161109 American Chemical Society, Washington, DC, US ISSN: 0002-7863 compound 3b --- -/--	1

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"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/25196

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H. SUZUKI, ET AL.: "Selective reduction with lithium aluminium hydride / diphosphorus tetraiodide" CHEMISTRY LETTERS, no. 6, June 1983 (1983-06), pages 909-910, XP002161110 Chemical Society of Japan, Tokyo, JP ISSN: 0366-7022 table 1, entries 5,14 ---	1
X	US 2 095 619 A (W.C. STOESEER, ET AL.) 12 October 1937 (1937-10-12) examples 1-6 ---	1
X	S. GOLDSCHMIDT, ET AL.: "Biphenyl derivatives II. Basic 4-biphenyl compounds" RECUEIL DES TRAVAUX CHIMIQUES DES PAYS-BAS., vol. 69, no. 9/10, September 1950 (1950-09), pages 1109-1117, XP002161111 Elsevier Science Publishers, Amsterdam, NL ISSN: 0165-0513 table I ---	1
X	W.F. COCKBURN, ET AL.: "Molecular rearrangement of tertiary amines. Part I" JOURNAL OF THE CHEMICAL SOCIETY, no. 8, August 1960 (1960-08), pages 3340-3346, XP002161112 Royal Society of Chemistry, Letchworth, GB page 3343, line 4 - line 5 -----	1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3 (in part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which part(s) of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons it appears impossible to execute a meaningful search and /or to issue a complete search report over the whole breadth of the claim(s). The search and the report for those claims can only be considered complete for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds as indicated in the relevant examples (1-287) and claims 4-26.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/25196

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9857934 A	23-12-1998	AU 7976998 A EP 0993448 A	04-01-1999 19-04-2000
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WO 9828269 A	02-07-1998	AU 5602098 A CN 1246847 A EP 0946508 A HR 970698 A LT 99076 A,B LV 12430 A LV 12430 B NO 992633 A PL 334250 A SI 20017 A US 6020357 A BR 9714073 A	17-07-1998 08-03-2000 06-10-1999 31-10-1998 25-02-2000 20-02-2000 20-07-2000 20-08-1999 14-02-2000 29-02-2000 01-02-2000 09-05-2000
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